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# RESPIRATORY CARE

A MONTHLY SCIENCE JOURNAL
41ST YEAR—ESTABLISHED 1956

SPECIAL ISSUE
Mechanical Ventilation: Ventilatory Techniques, Pharmacology, and Patient Management Strategies
Part II

- Revisiting HFV
- Exogenous Surfactant Therapy
- Partial Liquid Ventilation
- Inhaled NO in ARDS
- Pressure-Limited Ventilation
- Noninvasive Ventilation in ARF
- Conference Summary

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the inner nature

of things

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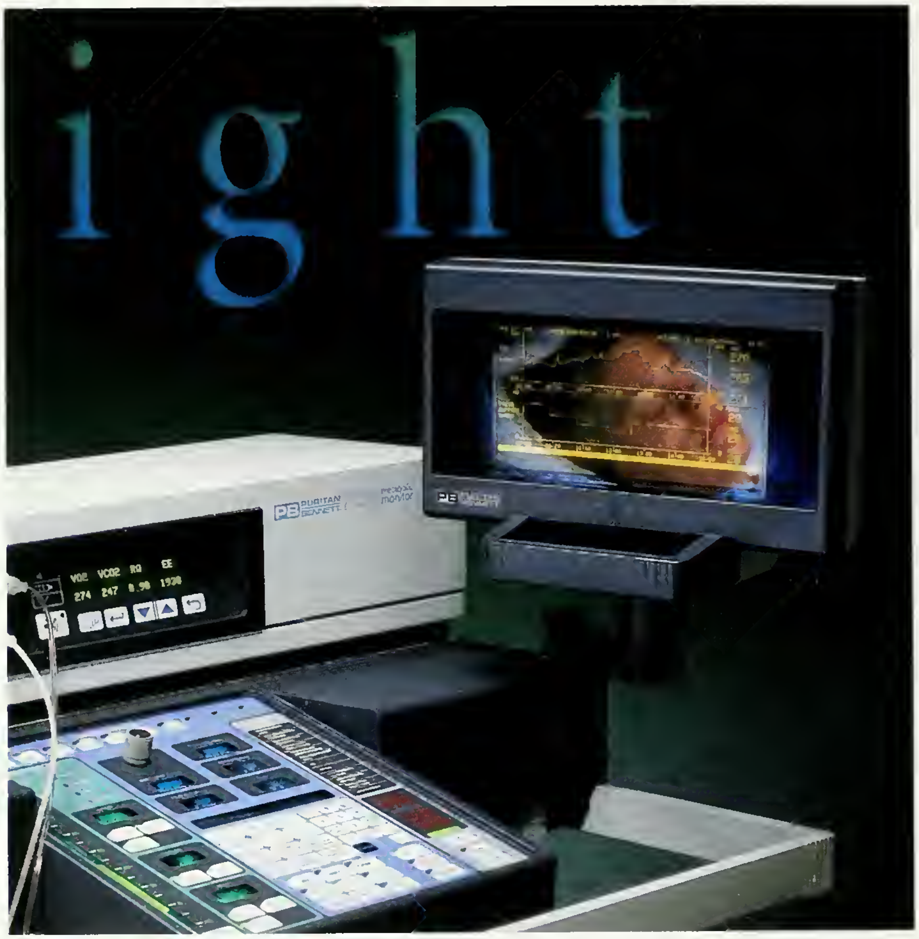

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in Cancún, Mexico

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### Editorials, Commentaries, and Reviews To Note

**Laryngeal Mask Airway and the ASA Difficult Airway Algorithm** (Review). JL Benumof. Anesthesiology 1996;84(3):686-699.

**Science Challenges the Dogmas of CPR** (Editorial). MH Weil. Chest 1996;109(3):597-598.

**Pulmonary Complications of Bone Marrow Transplantation** (Review). Chest 1996;109(4):1066-1077.

**Lung Reduction Surgery: Where Are We Heading?** (Editorial) M Cutaia. Chest 1996;109(4):866-868.

**Is Volume Reduction Surgery Appropriate in the Treatment of Emphysema?** (Editorial). **Yes.** JD Cooper, SS Lefrak. Am J Respir Crit Care Med 1996;153(4):1201-1204. **No.** BJ Make. Am J Respir Crit Care Med 1996;153(4):1205-1207.

**Health-Care Technology Assessment of Surgical Procedures: The Case of Reduction Pneumoplasty for Emphysema** (Pulmonary Perspective). GL Snider. Am J Respir Crit Care Med 1996;153(4):1208-1213.

**Clinical Diagnostic Criteria of the Adult Respiratory Distress Syndrome in the Intensive Care Unit**—DS Zaccardelli, EN Pattishall. Crit Care Med 1996;24(2):247.

OBJECTIVES: To determine the use of commonly used diagnostic criteria for adult/acute respiratory distress syndrome (ARDS), evaluate physiologic variables of most value in diagnosing ARDS, and assess the frequency of newly diagnosed ARDS. DESIGN: Self-administered questionnaire by mail. SETTING: Hospital intensive care units (ICUs). SUBJECTS: Intensive care physicians (n = 923) in the United States listed as ICU directors in the Society of Critical Care Medicine Membership Directory. INTERVENTIONS: None. MEASUREMENTS & MAIN RESULTS: A total of 448 (48.5%) physicians responded, with 301 questionnaires completed. Bilateral infiltrates on chest radiograph, the $P_{aO_2}/F_{IO_2}$ ratio, and pulmonary artery occlusion pressure were the most commonly used diagnostic criteria. However, the actual values used to diagnose ARDS were highly variable. The most important clinical physiologic variable used in determining the respiratory status of the ARDS patient was the $P_{aO_2}/F_{IO_2}$ ratio, followed by shunt fraction, alveolar-arterial oxygen tension gradient, $F_{IO_2}$, $P_{aO_2}$, respiratory system compliance, and minute ventilation. Respondents indicated that 9% of ICU beds at their institutions were occupied by a patient diagnosed with ARDS within the previous 7 days and 18.6% of all mechanically ventilated patients had ARDS by their own criteria. Based on the total number of ICU beds, the predicted incidence of ARDS would be ≅275,000 patients/year in the United States. CONCLUSION: A wide range of diagnostic criteria are utilized by clinicians in the diagnosis of ARDS.

**A Comparison between an Outpatient Hospital-Based Pulmonary Rehabilitation Program and a Home-Care Pulmonary Rehabilitation Program in Patients with COPD: A Follow-up of 18 Months**—JH Strijbos, DS Postma, R VanAltena, F Gimeno, GH Koëter. Chest 1996;109(2):366.

AIM: In this study, the effects of a 12-week hospital-based outpatient pulmonary rehabilitation program (HRP) are compared with those of a 12-week home-care rehabilitation program (HCRP) in COPD patients. A control group received no rehabilitation therapy. METHODS: After randomization and stratification, effects on lung function, exercise performance (4-min walking test and cycle ergometer test), dyspnea, and leg effort during exercise, and well-being were assessed in 45 COPD patients with moderate to severe airflow limitation (mean [SD] $FEV_1$ percent predicted, 42.8 [8.4]). RESULTS: After HRP and HCRP, at 3 to 6 months after the start of the study, equal improvements were detected in exercise capacity and in Borg dyspnea and leg effort scores at similar work levels during the cycle test. However, whereas after HRP at longer term values tended to return to baseline outcome, after HCRP a further ongoing significant improvement in exercise capacity was observed, while Borg dyspnea scores remained significantly improved over 18 months. Improvements in cycle workload and dyspnea score were significantly better maintained after HCRP as compared with HRP. Lung function, arterial oxygen saturation, and heart frequency during exercise did not change. A significant improvement in well-being was maintained over 18 months in both rehabilitation groups. CONCLUSION: Beneficial effects are achieved both after a HRP and a HCRP in COPD patients with moderate to severe airflow limitation. Yet we recommend to initiate HCRPs as improvements are maintained longer and are even further strengthened in this setting. *See the related editorial: **Pulmonary Rehabilitation: Does the Site Matter?**—HM Thomas III. Chest 1996;109(2):299-300.*

**An Education Program for Parents of Children with Asthma: Differences in Attendance between Smoking and Nonsmoking Parents**—L Fish, SR Wilson, DM Latini, NJ Starr. Am J Public Health 1996;86(2):246.

We studied smoking status in relation to parental attendance at an asthma education program for child patients of a health maintenance organization. Nonattendance rates were 24%, 42%, and 78% in nonsmoking, 1-smoker, and 2-or-more-smoker families, respectively, and 33% overall. Only the number of smokers (odds ratio [OR] =

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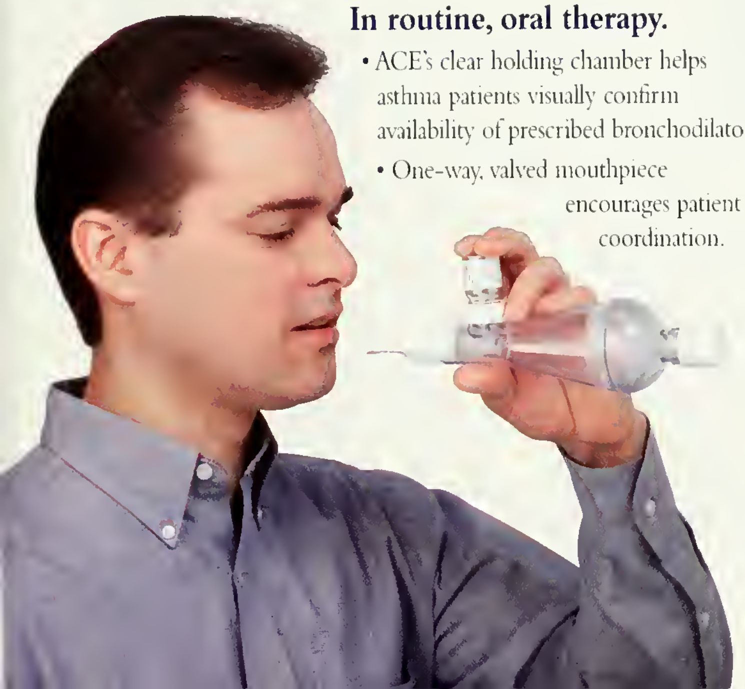

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[1] Harwood Robert, Rau Joseph, Thomas-Goodfellow Lynda. A Comparison of Three Methods of Metered Do[illegible] [illegible]very to a Mechanically Ventilated Adult Lung Model. *Respiratory Care* September 1994 Vol. 39 No. 9 p. 866

[2] Newman Stephen P, Pavia Demetri, Clarke Stewart W. Simple instructions for using pressurized aerosol [illegible] *[illegible]nal of the Royal Society of Medicine* November 1980 Vol. 73 p. 77[illegible]

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3.1; 95% confidence interval [CI] = 1.8, 5.3) and perceived adverse impact of asthma on the family (OR = 0.4; 95% CI = 0.2, 0.9) were retained in a multivariate model that correctly classified 73% of families; demographic characteristics, frequency of asthma symptoms, and health care use were rejected. There was a tendency for smoking parents to deny that their child had asthma (17% among families with 2 or more smokers; 9% among nonsmoking families). Asthma education programs may fail to involve parents who smoke.

**Regional Tracheal Blood Flow during Conventional and High-Frequency Jet Ventilation in Suckling Pigs**—KA Cavanagh, HF Hill, WV Wojciechowski, JC Parker. Crit Care Med 1996; 24(2):280.

OBJECTIVE: To determine whether intubation and ventilation with either conventional mechanical ventilation or high-frequency jet ventilation, using dry or humidified gas, could induce regional tracheal ischemia and serve as a basis for the tracheal necrosis observed clinically during ventilation. DESIGN: Prospective, multiple group, controlled experimental study. SETTING: Medical school research laboratory. SUBJECTS: Twenty, 3- to 5-week-old suckling pigs. INTERVENTIONS: Anesthetized, closed-chest piglets were intubated and ventilated for 30 minutes with conventional mechanical ventilation and then ventilated for 2 additional hours with either conventional mechanical ventilation or high-frequency jet ventilation. Groups were also ventilated, using both modes of ventilation, with either 37 °C humidified gas or 25 °C dry gas. MEASUREMENTS & MAIN RESULTS: Blood flow groups were compared during spontaneous breathing, conventional mechanical ventilation, high-frequency jet ventilation and both ventilation modes, using 37 °C humidified or 22 °C dry inspired gas. Groups were compared, using an analysis of variance with a Newman-Keul's posttest. Regional tracheal blood flow was measured, using radioactive microspheres. Cardiac output and organ blood flows were also monitored. Tracheal blood flow increased 10.3-fold within 30 minutes after intubation, but there were no significant differences in regional or total tracheal blood flow between conventional mechanical ventilation and high-frequency jet ventilation, using 37 °C humidified gas. Tracheal blood flow was increased further using high-frequency jet ventilation and 25 °C dry gas but not conventional mechanical ventilation with dry gas. Although ventilation reduced cardiac output by ≈30%, there were no significant differences in organ distribution between modes of ventilation. CONCLUSIONS: Acute tracheal hyperemia occurred with intubation and ventilation with both conventional mechanical ventilation and high-frequency jet ventilation but no differences were observed between ventilation modes. Hyperemia was further increased with cool, dry inspired gas, using high-frequency jet ventilation but not conventional mechanical ventilation. Although acute tracheal ischemia was not produced by high-frequency jet ventilation or conventional mechanical ventilation, factors which alter the balance between arterial supply and metabolic demand or induce inflammation may contribute to the tracheal necrosis reported during sustained ventilation.

**The Impact of Extracorporeal Membrane Oxygenation on Survival in Pediatric Patients with Acute Respiratory Failure**—TP Green, OD Timmons, JC Fackler, FW Moler, AE Thompson, MF Sweeney, for the Pediatric Critical Care Study Group. Crit Care Med 1996;24(2):323.

OBJECTIVE: Extracorporeal membrane oxygenation (ECMO) has been used with increasing frequency in the treatment of acute respiratory failure in pediatric patients. Our objective in this study was to test the hypothesis that ECMO improves outcome in pediatric patients with acute respiratory failure. DESIGN: Multicenter, retrospective cohort analysis. SETTING: Forty-one pediatric intensive care units participated in the study under the auspices of the Pediatric Critical Care Study Group. PATIENTS: All pediatric patients admitted to the participating institutions with acute respiratory failure during 1991 were included. Patients with congenital heart disease, contraindications to ECMO, or incomplete data were excluded, yielding a data set of 331 patients from 32 hospitals. INTERVENTIONS: Conventional mechanical ventilation, high-frequency ventilation, and extracorporeal membrane oxygenation. MEASUREMENTS & MAIN RESULTS: Multivariate logistic regression analysis was used to identify factors associated with survival. In a second analysis, pairs of ECMO and non-ECMO patients, matched by severity of disease and respiratory diagnosis, were compared. The use of ECMO ($p = 0.0082$), but not the use of high-frequency ventilation, was associated with a reduction in mortality. Other factors independently associated with mortality included oxygenation index ($p < 0.0001$), Pediatric Risk of Mortality score (PRISM) ($p < 0.0001$) and the $P_{aCO_2}$ ($p = 0.045$). In 53 diagnosis- and risk-matched pairs, there was a significantly lower mortality rate (26.4% vs 47.2%; $p < 0.01$) in the ECMO-treated patients. When all patients were stratified into mortality risk quartiles on the basis of oxygenation index and PRISM score, the proportion of deaths among ECMO-treated patients in the 50-75% mortality risk quartile was less than half the proportion in the non-ECMO treated patients (28.6% vs 71.4%; $p < 0.05$). No effect was seen in the other quartiles. CONCLUSIONS: The use of ECMO was associated with an improved survival in pediatric patients with respiratory failure. The lack of association of outcome with treatment in the ECMO-capable hospital or with another tertiary technology (ie, high-frequency ventilation) suggests that ECMO itself was responsible for the improved outcome. Further studies of this procedure are warranted but require broad-based multi-institutional participation to provide sufficient statistical power and sensitivity to demonstrate efficacy.

**Effectiveness of Nitric Oxide Inhalatinn in Septic ARDS**—P Krafft, P Fridrich, RD Fitzgerald, D Koc, H Steltzer. Chest 1996;109(2):486.

OBJECTIVE: To evaluate the percentage of nitric oxide (NO) responders in septic shock patients with ARDS. Additionally, to investigate long-term NO effects on cardiac performance and oxygen kinetic patterns in NO responders versus nonresponders. DESIGN: Prospective cohort study. SETTING: ICU of a university hospital. PATIENTS: Twenty-five consecutive patients with a diagnosis of septic shock and established ARDS requiring inotropic and vasopressor support. INTERVENTIONS: After diagnosis of ARDS, NO was administered at 18 or 36 ppm. Patients demonstrating a NO-induced rise of arterial oxygen tension of 20% or more and/or a fall in mean pulmonary artery pressure of 15% or more were grouped as NO responders; others were grouped as nonresponders. MEASUREMENTS & RESULTS: Ten patients (40%) were NO responders, while 15 patients (60%) were nonresponders. Mortality was 40% in NO responders and 67% in nonresponders (NS). NO responders developed a significantly lower mean pulmonary artery pressure (28 ± 6 vs 33 ± 6 mm Hg; $p < 0.05$), lower pulmonary vascular resistance (PVR: 258 ± 73 vs 377 ± 163 $\text{dyne} \cdot \text{s} \cdot \text{cm}^{-5} \cdot \text{m}^{-2}$; $p < 0.05$), and higher $P_{aO_2}/F_{IO_2}$ ratio (192 ± 85 vs 144 ± 74 mm Hg; $p < 0.05$) within the study period. In responders, NO-induced afterload reduction resulted in increased right ventricular ejection fraction (RVEF: 40 ± 7 vs 35 ± 9%; $p < 0.05$), significantly higher cardiac index (CI, 4.5 ± 1.1 vs 4.0 ± 1.2 $\text{L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$; $p < 0.05$) and oxygen delivery ($\dot{D}_{O_2}$: 681 ± 141 vs 599 ± 160 $\text{ml} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$; $p < 0.05$) compared with nonresponders. In NO nonresponders, RVEF was correlated with PVR, CI, $\dot{D}_{O_2}$, mixed venous oxygen saturation ($S_{\bar{v}O_2}$), and oxygen extraction ratio ($O_2ER$) ($r = \pm 0.60$ to $\pm 0.69$; $p < 0.05$). No significant correlation between RVEF and any of these parameters was observed in responders. $S_{\bar{v}O_2}$ (75 ± 7 vs 69 ± 8%; $p < 0.05$) and $O_2ER$ (0.24 ± 0.06 vs 0.27 ± 0.06; $p < 0.05$) were significantly different between responders and nonresponders, while no difference in oxygen consumption was observed (161 ± 41 vs 153 ± 43 $\text{ml} \cdot \text{min} \cdot \text{m}^{-2}$). CONCLUSIONS: Inhaled NO is effective in only a subgroup of septic ARDS patients, with a higher, but nonsignificantly different percentage of survivors in the responder group. NO responders were characterized by increased RVEF accompanied by higher CI, $\dot{D}_{O_2}$, and lower $O_2ER$. In nonresponders, RVEF remained depressed, with a close correlation between RVEF and CO as well as $\dot{D}_{O_2}$ and $O_2ER$. Thus, nonresponders seem to suffer from impaired cardiac reserves and correspondingly lower oxygen transport variables.

**Reduction Pneumoplasty for Giant Bullous Emphysema: Implications for Surgical Treatment of Nonbullous Emphysema**—GL Snider. Chest 1996;109(2):540.

A review of the literature on reduction pneumoplasty for giant bullous emphysema was undertaken to identify current criteria for this surgical treatment and in the hope of obtaining insights into evaluating reduction pneumoplasty for nonbullous emphysema. Twenty-two retrospective case series, published since 1950, were retrieved by a computer search of the literature and a search of the *Index Medicus* prior to 1966. Reduction pneumoplasty is most effective when bullae are larger than one third of a hemithorax with evidence of compression of adjacent lung tissue and an $FEV_1$ of less than 50% predicted; the presence of emphysema in nonbullous lung and the amount of compression are best judged by CT. The rationale for reduction pneumoplasty for nonbullous emphysema is supported by the similar early functional changes after reduction pneumoplasty for bullous and nonbullous—improvement of blood gas values and lung mechanics. A single study showing that decline of lung function after surgery for bullous emphysema was less in those who stopped smoking than in those who continued to smoke supports the need for preoperative and maintained smoking cessation in patients receiving reduction pneumoplasty. After 4 decades, the duration of improvement in lung function, whether worsening of emphysema occurs in remaining lung, and late morbidity and mortality after reduction pneumoplasty for bullous emphysema are not well defined. A registry with an unoperated-on comparison group could more rapidly accumulate such data after reduction pneumoplasty for nonbullous emphysema.

**Uncertain Value of Electronic Fetal Monitoring in Predicting Cerebral Palsy**—KB Nelson, JM Dambrosia, TY Ting, JK Grether. N Engl J Med 1996;334(10):613.

BACKGROUND: Electronic monitoring of the fetal heart rate is commonly performed, in part to detect hypoxia during delivery that may result in brain injury. It is not known whether specific abnormalities on electronic fetal monitoring are related to the risk of cerebral palsy. METHODS: Among 155,636 children born from 1983 through 1985 in 4 California counties, we identified singleton infants with birthweights of at least 2,500 g who survived to 3 years of age and had moderate or severe cerebral palsy. The children with cerebral palsy were compared with randomly selected control children with respect to characteristics noted in the birth records. RESULTS: Seventy-eight of 95 children with cerebral palsy and 300 of 378 controls underwent intrapartum fetal monitoring. Characteristics found to be associated with an increased risk of cerebral palsy were multiple late decelerations in the heart rate, commonly defined as slowing of the heart rate well after the onset of uterine contractions (odds ratio, 3.9; 95% confidence interval, 1.7 to 9.3), and decreased beat-to-beat variability of the heart rate (odds ratio, 2.7; 95% confidence interval, 1.1 to 5.8); there was no association between the highest or lowest fetal heart rate recorded for each child and the risk of cerebral palsy. Even after adjustment for other risk factors, the association of abnormalities in fetal monitoring with an increased risk of cerebral palsy persisted (adjusted odds ratio, 2.7; 95% confidence interval, 1.4 to 5.4). The 21 children with cerebral palsy who had multiple late decelerations or decreased variability in heart rate on fetal monitoring represented only 0.19% of singleton infants with birthweights of 2,500 g or more who had these fetal monitoring findings, for a false positive rate of 99.8%. CONCLUSIONS: Specific abnormal findings on electronic monitoring of the fetal heart rate were associated with an increased risk of cerebral palsy. However, the false positive rate was extremely high. Since cesarean section is often performed when such abnor-

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malities are noted and is associated with risk to the mother, our findings arouse concern that, if these indications were widely used, many cesarean sections would be performed without benefit and with the potential for harm. *See the related editorial: **Cerebral Palsy and Intrapartum Fetal Monitoring**. D MacDonald. N Engl J Med 1996; 334(10):659-660.*

**Pulmonary Hemodynamics in the Obstructive Sleep Apnea Syndrome: Results in 220 Consecutive Patients**—A Chaouat, E Weitzenblum, J Krieger, M Oswald, R Kessler. Chest 1996;109 (2):380.

We have investigated pulmonary hemodynamics in a large series of consecutive, unselected patients with obstructive sleep apnea syndrome (OSAS). The aims of this study were to evaluate the frequency of pulmonary artery hypertension (PH) in OSAS and to analyze, as far as possible, its mechanisms. Two hundred twenty patients were included on the basis of a polysomnographic diagnosis of OSAS (apnea + hypopnea index > 20). PH, defined by a resting mean pulmonary artery mean pressure (PAP) of at least 20 mm Hg, was observed in 37 of 220 patients (17%). Patients with PH differed from the others with regard to pulmonary volumes (vital capacity [VC], $FEV_1$) and the $FEV_1$/VC ratio that were significantly lower ($p < 0.001$); $P_{aO_2}$ (64.4 ± 9.3 vs 74.7 ± 10.1 mm Hg; $p < 0.001$), $P_{aCO_2}$ (43.8 ± 5.4 vs 37.6 ± 3.9 mm Hg; $p < 0.001$), apnea + hypopnea index (100 ± 33 vs 74 ± 32; $p < 0.001$), and mean nocturnal arterial oxygen saturation ($S_{aO_2}$) (88 ± 6% vs 94 ± 2%; $p < 0.001$). Patients with PH were also more overweight ($p < 0.001$). Multiple regression analysis showed that 50% of the variance of PAP could be predicted by an equation including $P_{aCO_2}$ (accounting for 32% of the variance), $FEV_1$ (12%), airway resistance (4%), and mean nocturnal $S_{aO_2}$ (2%). In conclusion, PH is observed, in agreement with previous studies, in less than 20% of OSAS patients. PH is strongly linked to the presence of an obstructive (rather than restrictive) ventilatory pattern, hypoxemia, and hypercapnia, and is generally accounted for by an associated obstructive airways disease. In this regard, the severity of OSAS plays only a minor role. *See the related editorial: **Sleep Apnea and Pulmonary Hypertension**—DS Dark. Chest 1996;109(2):300-301.*

**Advance Directive Education during Pulmonary Rehabilitation**—JE Heffner, B Fahy, C Barbieri. Chest 1996;109(2):373.

We conducted a questionnaire survey of 346 pulmonary rehabilitation programs to determine the present utilization and potential value of these sites for promoting advance directive education for patients with chronic lung diseases. Responses were analyzed for all responding programs and for programs categorized by size. Eighty-two percent of the 218 responding programs discussed with patients prognostic information. Only 33% of programs asked patients if they had advance directives and 17% kept these documents on file. Thirty-three percent of programs provided some form of advance directive education, and 42% distributed directive educational material, usually through informal and unstructured methods. Seventy-seven percent of responders considered pulmonary rehabilitation an appropriate site for directive education, and 86% indicated willingness to incorporate directive education into their programs. Larger programs were more likely to present information about patient prognosis ($p = 0.0003$) and advance directives ($p = 0.021$). We conclude that most of the responding pulmonary rehabilitation programs do not educate patients about advance directives but are willing to do so if supplied with appropriate teaching materials. Rehabilitation programs may be valuable sites for educating patients with chronic disorders about advance directives and promoting an improved patient-physician dialogue about these issues. *See the related editorial: **Are Advance Directives Becoming an Endangered Species?**—HS Perkins. Chest 1996;109 (2):299.*

**Nosocomial Pneumonia and Mortality among Patients in Intensive Care Units**—JY Fagon, J Chastre, A Vuagnat, JL Trouillet, A Novara, C Gibert. JAMA 1996;275(11):866.

OBJECTIVE: To evaluate the role that nosocomial pneumonia plays in the outcome of intensive care unit (ICU) patients. DESIGN: Cohort study. SETTING: Medical ICU, Hôpital Bichat, Paris, France, an academic tertiary care center. PATIENTS: A total of 1,978 consecutive patients admitted to the ICU for at least 48 hours. MAIN OUTCOME MEASURES: Various parameters known to be strongly associated with death of ICU patients were recorded: age, location before admission to the ICU, diagnostic categories, Acute Physiology and Chronic Health Evaluation (APACHE) II score, Simplified Acute Physiology Score, McCabe score, number and type of dysfunctional organs, and the development of nosocomial bacteremia and nosocomial urinary tract infection. These variables and the presence or absence of nosocomial pneumonia were compared between survivors and nonsurvivors and entered into a stepwise logistic regression model to evaluate their independent prognostic roles. RESULTS: Nosocomial pneumonia developed in 328 patients (16.6%) whose mortality rate was 52.4% compared with 22.4% for patients without ICU-acquired pneumonia ($p < 0.001$). APACHE II score (odds ratio [OR] = 1.08; 95% confidence interval [CI], 1.06 to 1.10; $p < 0.001$), number of dysfunctional organs (OR = 1.54; 95% CI, 1.36 to 1.74; $p < 0.001$), nosocomial pneumonia (OR = 2.08; 95% CI, 1.55 to 2.80; $p < 0.001$), nosocomial bacteremia (OR = 2.51; 95% CI, 1.78 to 3.55; $p < 0.001$), ultimately or rapidly fatal underlying disease (OR = 1.76; 95% CI, 1.38 to 2.25; $p < 0.001$), and admission from another ICU (OR = 1.30; 95% CI, 1.01 to 1.68; $p = 0.04$) were significantly associated with mortality. CONCLUSION: These data suggest that, in addition to the severity of underlying medical conditions and nosocomial bacteremia, nosocomial pneumonia independently contributes to ICU patient mortality.

**Effect of Frequency of Prenatal Care Visits on Perinatal Outcome among Low-Risk Women: A Randomized Controlled Trial**—RS McDuffie Jr, A Beck, K Bischoff, J Cross, M Orleans. JAMA 1996;275(11):847.

OBJECTIVES: In 1989, the Expert Panel on the Content of Prenatal Care established guidelines on the timing and content of prenatal care, including a schedule consisting of fewer prenatal visits than traditionally provided, for women at low risk of adverse perinatal outcomes. We tested the hypothesis that there are no significant increases in adverse perinatal outcomes when low-risk women are seen in a prenatal care visit schedule of fewer visits than routinely advised. DESIGN. Randomized controlled trial. SETTING: Group-model health maintenance organization. PATIENTS: A total of 2,764 pregnant women, judged to be at low risk of adverse perinatal outcomes. INTERVENTIONS: Following risk assessment, participants were randomly assigned to an experimental schedule (9 visits) or a control schedule (14 visits) with additional visits as indicated or as desired by the patient. MAIN OUTCOME MEASURES: Preterm delivery, preeclampsia, cesarean delivery, low birthweight, and patients' satisfaction with care. RESULTS: On average, there were 2.7 fewer visits observed in the experimental group than in the control group. There were no significant increases in the main outcomes of the experimental group: preterm delivery (relative risk [RR], 1.08; 95% confidence interval [CI], 0.92 to 1.27; $p = 0.19$), pre-eclampsia (RR, 0.94; 95% CI, 0.78 to 1.14; $p = 0.74$), cesarean delivery (RR, 1.04; 95% CI, 0.93 to 1.17; $p = 0.25$), and low birthweight (RR, 0.94; 95% CI, 0.78 to 1.12; $p = 0.76$). There were no differences between the 2 groups in patients' satisfaction with quality of prenatal care. CONCLUSION: In this study, good perinatal outcomes and patient satisfaction were maintained when the prenatal visit schedule proposed by the Expert Panel on the Content of Prenatal Care was observed.

**Low Flow Oxygen Delivery via Nasal Cannula to Neonates**—NN Finer, R Bates, P Tomat. Pediatr Pulmonol 1996;21:48.

Neonates with chronic lung disease often require oxygen in the neonatal intensive care unit. The purpose of this study was to determine (1) the actual inspired oxygen concentration ($F_{IO_2}$) delivered to neonates when using a low-flow flowmeter and a nasal cannula, and (2) the accuracy with which $F_{IO_2}$ could be estimated using a formula that

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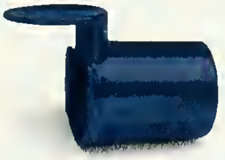

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REFERENCES 1 Data on file. HealthScan Products Inc. 2 Wheeler BB, Bollers NE. Initial experience with a novel spacer device (Presented at the 1993 meeting of the American Academy of Allergy and Immunology). * U.S Patent No 5,040,527 OA760004 0 © 1994 HealthScan Products Inc

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we developed. We studied 2 groups of infants: 18 infants less than 1,500 g and 13 infants greater than 1,500 g. We measured pharyngeal oxygen levels by sampling pharyngeal gas in infants receiving 100% humidified oxygen by nasal cannula from a low range flow flowmeter. The oxygen flow was increased by 25 mL/min increments from 25 to 200 mL/min. The measured $F_{IO_2}$ was compared with the calculated $F_{IO_2}$ using the formula:

$$F_{IO_2} \text{ measured} = \text{oxygen flow } (\text{mL/min} \times 0.79) + (0.21 \times \dot{V}_E \times 100/\dot{V}_I$$

where minute ventilation ($\dot{V}_E$) equals the minute ventilation in mL/min ($\dot{V}_E = V_T \times$ respiratory rate). For both groups of infants, increments of 25 mL/min of flow produced distinctive changes in $F_{IO_2}$ at all levels ($p < 0.001$). The calculated $F_{IO_2}$ did not significantly differ from the actual $F_{IO_2}$ at any flow. The calculated $F_{IO_2}$ was most predictive when using an assumed tidal volume of 5.5 mL/kg. We conclude that an accurate flowmeter connected to 100% humidified oxygen can produce a wide range of predictable $F_{IO_2}$s for neonates, especially those with birthweights of less than 1,500 g. The proposed formula allows useful estimation of the infant's $F_{IO_2}$ when we assume a tidal volume of 5.5 mL/kg.

**Guidelines for the Use of Nebulizers in the Home and at Domiciliary Sites: Report of a Consensus Conference**—WJ O'Donohue, Jr, the National Association for Medical Direction of Respiratory Care (NAMDRC) Consensus Group. Chest 1996;109:814.

Guidelines for the use of nebulizers outside of the hospital were developed at the request of the Health Care Financing Administration (HCFA) to assist in the preparation of Medicare criteria for reimbursement. The National Association for Medical Direction of Respiratory Care (NAMDRC) convened a consensus conference in Leesburg VA, with physician representatives from the major medical organizations involved in adult and pediatric respiratory care. Members of the health-care industry also were invited to participate. After review of the pertinent references, members of the faculty were preassigned topics for presentations during the first day of the meeting. Three workshops were organized to address segments of the consensus statement and to develop written reports. Each report was reviewed by the entire group and then finalized. The Consensus Conference recommends that a metered-dose inhaler (MDI) with reservoir chamber is the preferred mode of aerosol therapy for patients outside of the hospital. The circumstances under which a small-volume nebulizer (SVN) may be appropriate are described. The medications that may be administered by SVN are identified with recommendations as to the usual doses to be prescribed. A cost analysis of the various modes of aerosol therapy is presented. These guidelines should be of value to physicians who are prescribing aerosol therapy in the home and also to policy makers who are developing guidelines for reimbursement.

**A Placebo-Controlled Trial of Prostacyclin in Acute Respiratory Failure in COPD**—SL Archer, D Mike, J Crow, W Long, EK Weir. Chest 1996;109(3):750.

Although patients with COPD often have elevated pulmonary artery pressures (PAP) and pulmonary vascular resistance (PVR), it is uncertain whether treatment of this pulmonary hypertension is beneficial. We evaluated the extent of pulmonary hypertension in 16 patients with severe COPD complicated by acute respiratory failure and pulmonary hypertension. We assessed the hypothesis that the vasodilator prostacyclin ($PGI_2$) would reduce PVR and improve systemic $O_2$ transport. Patients with a COPD exacerbation requiring mechanical ventilation, and mean PAP greater than 30 mm Hg, were randomized to receive $PGI_2$ or placebo, in addition to conventional therapy. Randomization to $PGI_2$ or placebo therapy occurred 1 to 12 hours after intubation, while the patient was mechanically ventilated. An optimal $PGI_2$ dose (2 to 12 ng/kg/min, I.V.) was established in an initial dose-ranging study and then this dose was infused continuously for 48 hours. $PGI_2$ initially reduced PVR, but this effect dissipated within 24 hours, indicating the development of tachyphylaxis. Tolerance to the adverse effects of $PGI_2$ (tachycardia, hypotension, flushing, and headache) also developed over time. $PGI_2$ treatment was associated with a significant fall in $P_{aO_2}$ but no increase in systemic oxygen transport. $PGI_2$ proved to be a nonselective vasodilator that caused mild hypoxemia. Despite acute respiratory failure, pulmonary hypertension is mild in patients with severe COPD receiving mechanical ventilation, and I.V. $PGI_2$ is not beneficial in such patients.

**Survey of Asthma Practice among Emergency Physicians**—CL Emerman, RK Cydulka, E Skobeloff. Chest 1996;109(3):708.

PURPOSE: The National Asthma Education and Prevention Program (NAEPP) published guidelines for asthma management in 1991. The purpose of this study is to assess the concordance between emergency physicians' practice and the guidelines. DESIGN: Survey mailed to emergency physicians. Nonrespondents were mailed a second copy of the survey. PARTICIPANTS: Eight hundred randomly selected active members of the American College of Emergency Physicians. INTERVENTIONS: None. MEASUREMENTS: Participants were asked questions regarding training, current asthma practices, and sources of information on asthma management. RESULTS: Eight hundred questionnaires were mailed, of which 416 (52%) were returned. Sixty-four percent of respondents administer $\beta$-agonists consistent with the NAEPP guidelines. Seventy-five percent of respondents administer corticosteroids in similar accord, while 75% prescribed outpatient corticosteroids in concordance with those recommendations. Forty-seven percent report measuring pretreatment pulmonary function more than half the time and only 38% report checking pulmonary function prior to disposition more than half the time. CONCLUSIONS: Most emergency physicians surveyed use $\beta$-agonists and steroids at least as often as recommended. A minority of emergency physicians reported utilizing pulmonary function testing in the manner recommended by the NAEPP. *See the related editorial: **Guidelines in Need of Guidance**. A Sarwar, RD Brandstetter. Chest 1996;109(3):594-595.*

**The Association between Parental Smoking and the Diet Quality of Low-Income Children**—RK Johnson, MQ Wang, MJ Smith, G Connolly. Pediatrics 1996;97(3):312.

OBJECTIVE: To assess the association between parental smoking and the diet quality of children residing in low-income households in the United States. METHODS: Data from 515 low-income children (≤ 185% of the poverty line), ages 2 to 17, who participated in the 1989 and 1990 United States Department of Agriculture Continuing Survey of Food Intakes of Individuals were examined. Diet quality was assessed by examining the average daily amount of nutrients consumed per 1,000 kcal for protein, fiber, and 14 essential vitamins and minerals as well as total energy, percent of energy from total fat and saturated fat, and cholesterol and sodium intakes using the 3-day average of one 24-hour recall and 2 days of diet records. Parental smoking was categorized as 4 levels (nonsmoker; 1 to 10, 11 to 20, and more than 20) on the basis of the average number of cigarettes smoked per day by the sample child's parents. Analysis of covariance examined differences in the children's nutrient intake among the 4 smoking categories while controlling for race, mother's age and occupation, child age, and sex. RESULTS: Low-income children with parents who smoked ($n = 235$) were more likely to be white ($p < 0.001$), had younger mothers ($p < 0.05$), and were more likely to have mothers employed in blue-collar occupations ($p < 0.001$) than children whose parents were nonsmokers ($n = 280$). Children whose parents smoked 11 or more cigarettes per day had lower vitamin A intakes and higher total energy and sodium intakes than children whose parents smoked 10 or fewer cigarettes/day. Children whose parents smoked more than 20 cigarettes/day had a higher percentage of energy from saturated fat, and children whose parents smoked 11 to 20 cigarettes/day had the highest cholesterol intakes in comparison with the rest of the sample. Parental smoking was also related to total fiber intake per 1,000 kcal, with children of smokers having lower fiber intakes than children of nonsmokers. CONCLUSIONS: On average, low-income children of smokers had

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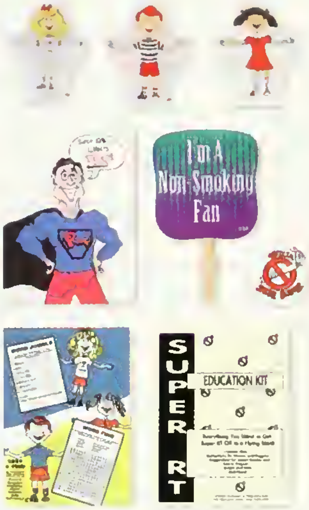

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a poorer diet quality than low-income children of nonsmokers, thus increasing their future risk of chronic disease.

**Fundus Pigmentation in Retinopathy of Prematurity**—T Monos, SD Rosen, M Karplus, Y Yassur. Pediatrics 1996;97:343.

OBJECTIVE: A prospective study design was used to investigate the association between different degrees of fundus pigmentation and the incidence of retinopathy of prematurity (ROP) among very low birthweight infants in a large neonatal intensive care unit. METHODS: The study group consisted of 161 infants, weighing 1,500 g or less at birth and included all infants born from 1988 to 1990 who survived at least 10 weeks. Presence or lack of any acute stage ROP was determined by weekly ophthalmologic examination from the age of 4 weeks. The degree of fundus pigmentation was recorded for each infant during the first examination. RESULTS: Infants with dark fundus pigmentation were found to be at half the risk of developing ROP as compared with the infants having light/medium fundus pigmentation (relative risk = 0.5; 95% confidence interval = 0.2 - 1.1) When controlling for birthweight, gestational age, length of oxygen therapy, and ethnic group in multivariate analysis, dark pigmentation was an independent and statistically significant protective factor (odds ratio = 0.09, 95% confidence interval = 0.02 – 0.6). None of the infants with Stage III ROP or higher had dark pigmentation. CONCLUSION: We speculate that large amounts of melanin in the retinal pigment epithelium or choroid may protect the dark-pigmented very low-birthweight infant from developing ROP.

**Apparent Life-Threatening Events in Presumed Healthy Neonates during the First Three Days of Life**—LJ Grylack, AD Williams. Pediatrics 1996;97(3):349.

OBJECTIVE: To study the historical, clinical, and pneumographic correlates of apparent life-threatening events (ALTEs) in a term newborn nursery population during the first 3 days of life in a maternity hospital. METHODS: Twenty newborns with ALTEs during the first 3 days of life were studied. Family, antenatal, and intrapartum histories were reviewed. Diagnostic and therapeutic data surrounding the ALTEs were documented. Multichannel recordings performed after the ALTEs occurred were analyzed. Hospital discharge dispositions and postdischarge outcomes were reviewed. RESULTS: Of approximately 15,000 deliveries during a 3-year period, 20 infants had ALTEs. Apnea was the most common presenting symptom, and cyanosis usually accompanied the event. Tactile stimulation and oxygen were the most frequent acute treatments, with airway clearance, intermittent positive pressure ventilation, and cardiac massage less common. Forty percent of the events had potentially identifiable causes, including central nervous system abnormality, airway obstruction, or a persistent fetal cardiovascular shunt. Of the initial multichannel recordings, 11 had desaturation of less than 85%, 10 had apneic pauses of greater than 15 seconds, and 4 had bradycardia of less than 80 beats/min. Eighteen infants were discharged and received home monitors; 4 received medication. ALTEs recurred in 4 infants before discharge and in 1 after discharge. No deaths occurred. CONCLUSIONS: (1) ALTEs do occur in the early newborn period in a low-risk term group; (2) causes are unknown in the majority of cases; (3) multichannel recordings may have abnormalities; and (4) the likelihood of recurrent ALTEs is greater during the first week than during the next 2 months.

**Inhaled Nitric Oxide for High-Altitude Pulmonary Edema**—U Scherrer, L Vollenweider, A Delabays, M Savcic, U Eichenberger, GR Kleger, A Fikrle, PE Ballmer, P Nicod, P Bärtsch. N Engl J Med 1996;334(10):624.

BACKGROUND: Pulmonary hypertension is a hallmark of high-altitude pulmonary edema and may contribute to its pathogenesis. When administered by inhalation, nitric oxide, an endothelium-derived relaxing factor, attenuates the pulmonary vasoconstriction produced by short-term hypoxia. METHODS. We studied the effects of inhaled nitric oxide on pulmonary-artery pressure and arterial oxygenation in 18 mountaineers prone to high-altitude pulmonary edema and 18 mountaineers resistant to this condition in a high-altitude laboratory (altitude, 4,559 m). We also obtained lung-perfusion scans before and during nitric oxide inhalation to gain further insight into the mechanism of action of nitric oxide. RESULTS. In the high-altitude laboratory, subjects prone to high-altitude pulmonary edema had more pronounced pulmonary hypertension and hypoxemia than subjects resistant to high-altitude pulmonary edema. Arterial oxygen saturation was inversely related to the severity of pulmonary hypertension ($r = -0.50$, $p = 0.002$). In subjects prone to high-altitude pulmonary edema, the inhalation of nitric oxide (40 ppm for 15 min) produced a decrease in mean ± SD systolic pulmonary-artery pressure that was 3 times larger than the decrease in subjects resistant to such edema (25.9 ± 8.9 vs 8.7 ± 4.8 mm Hg, $p < 0.001$). Inhaled nitric oxide improved arterial oxygenation in the 10 subjects who had radiographic evidence of pulmonary edema (arterial oxygen saturation increased from 67 ± 10 to 73 ± 12%, $p = 0.047$), whereas it worsened oxygenation in subjects resistant to high-altitude pulmonary edema. The nitric oxide-induced improvement in arterial oxygenation in subjects with high-altitude pulmonary edema was accompanied by a shift in blood flow in the lung away from edematous segments and toward nonedematous segments. CONCLUSIONS. The inhalation of nitric oxide improves arterial oxygenation in high-altitude pulmonary edema, and this beneficial effect may be related to its favorable action on the distribution of blood flow in the lungs. A defect in nitric oxide synthesis may contribute to high-altitude pulmonary edema. *See the related editorial:* ***High-Altitude Pulmonary Edema****. EH Jerome, JW Severinghaus. N Engl J Med 1996;334(10):662-663.*

**Incidence of Anaerobes in Ventilator-Associated Pneumonia with Use of a Protected Specimen Brush**—P Doré, R Robert, G Grollier, J Rouffineau, H Lanquetot, JM Charrière, JL Fauchère. Am J Respir Crit Care Med 1996;153(4):1292.

The role of anaerobic bacteria in ventilator-associated pneumonia (VAP) has been little investigated. In this study we analyzed the incidence of anaerobes in patients with a first episode of bacteriologically documented VAP ($> 10^3$ CFU/mL), using protected specimen brushes (PSB). We particularly took care to preserve anaerobic conditions during transport and the microbiological procedure. Two groups were considered: group A with anaerobic bacteria recovered from PSB, with or without aerobes, and group B with aerobic bacteria only. One hundred and thirty patients were included, 30 (23%) in group A, and 100 (77%) in group B. The main anaerobic strains isolated were *Prevotella melaninogenica* (36%), *Fusobacterium nucleatum* (17%), and *Veillonella parvula* (12%). Univariate analysis demonstrated that patients in group A were younger than those in group B ($p < 0.05$) and their simplified acute physiologic score was higher ($p < 0.02$). The percentage of patients receiving antibiotics before PSB did not differ significantly between group A (57%) and group B (35%). VAP with anaerobes occurred more often in patients orotracheally intubated than nasotracheally intubated ($p < 0.02$). Episodes of VAP involving anaerobic bacteria occurred more often in the first 5 days (early VAP) than after the fifth day (late VAP) ($p < 0.05$). The 3-month mortality rate was similar in the 2 groups, but death occurred earlier in group B ($p < 0.01$). Multivariate analysis demonstrated that presence of altered level of consciousness ($p = 0.0002$), higher simplified acute physiologic score ($p = 0.003$), and admission to the medical ICU ($p = 0.02$) were the factors independently predisposing to the development of VAP with anaerobes.

**The Effect of Inspiratory Maneuvers on Expiratory Flow Rates in Health and Asthma: Influence of Lung Elastic Recoil**—JS Wanger, DN Ikle, RM Cherniack. Am J Respir Crit Care Med 1996;153(4):1302.

We studied the effect of breath holding and inspiratory speed on airflow during the FVC maneuver in 7 healthy subjects and 8 patients with asthma. The purpose of the study was to determine whether the effects of inspiratory speed and breath holding on expiratory flow were greater in patients with asthma than in healthy individuals; whether these effects were lessened by inhalation of aerosolized bronchodilator in the patients with asthma; and whether there was a relationship between the lung elastic recoil pressure and the expiratory flow achieved during 4 different maneuvers. We found that peak expiratory flow rate (PEFR) was significantly lower after both a slow inspiration and a breath hold than after a fast inspiration without a breath hold. In addition, a breath hold was associated with a significantly lower FEV$_1$. The effects of inspiratory speed and breath holding in the patients with asthma were not significantly different from those observed in the healthy subjects. There was a significant relationship between lung elastic recoil pressure at the point of onset of the FVC maneuvers (Pel Blow) and expiratory flow in both healthy and asthmatic subjects. Also, the decrease in Pel Blow with equivalent breath-hold time was greater in asthmatic subjects, which is consistent with an increase in viscoelastic elements in the lung. These findings corroborate previous suggestions that inspiratory speed and the duration of breath holding have significant implications in the performance of spirometry and peak flow measurements, and indicate the importance of standardization of the preceding inspiration when determining FEV$_1$ and PEFR.

**Standardization of Multiple Spirometers at Widely Separated Times and Places**—WS Linn, JC Solomon, H Gong Jr, EL Avol, WC Navidi, JM Peters. Am J Respir Crit Care Med 1996; 153(4):1309.

We designed a system for a multiyear longitudinal study of lung function in 12 widely separated communities, intending to minimize variation in instrument-related data. We used multiple rolling-seal spirometer/personal computer systems. Calibrations were checked before, during, and after each day's field testing, using multiple calibration syringes with electronic readouts. The syringes were rotated to obtain data for each syringe-spirometer combination. Before and after each annual field testing season, a laboratory reference spirometer system was calibrated against a water-displacement device and an electronic frequency counter, and then compared against each field spirometer and syringe. Field equipment consistently met American Thoracic Society (ATS) specifications. Variance among spirometers exceeded variance among syringes. A spirometer occasionally changed its volume readout by ≅ 1 to 2%. More rarely, a syringe changed its delivered volume by ≅ 1%. Syringes' electronic readouts tracked changes in delivered volume. Syringe readouts were the most stable component of the system, and were more reproducible than the laboratory water-displacement calibration. We conclude that variation in spirometers may limit the reliability of epidemiologic findings, even when these spirometers meet ATS specifications. Frequent calibration checks, traceable to an independent standard, and adjustment of individual test results can reduce measurement error.

**The Effect of Sleep Fragmentation on Daytime Function**—SE Martin, HM Engleman, IJ Deary, NJ Douglas. Am J Respir Crit Care Med 1996;153 (4):1328.

Patients with the sleep apnea/hypopnea syndrome suffer from impaired daytime function. This has been attributed to both sleep fragmentation and hypoxemia. To help understand which is causal we studied the effects of sleep fragmentation alone on daytime function. Sixteen normal subjects were studied on 2 pairs of 2 nights. The first night of each pair was for acclimatization, and on the second the subject either slept undisturbed or had sleep fragmented with sound pulses every 2 minutes. Sound volume and duration was titrated to cause a return to theta or alpha rhythm on the EEG for at least 3 seconds. Study nights were followed by daytime testing of psychometric function and mood and by a multiple sleep latency test (MSLT) and a maintenance of wakefulness test (MWT). Total sleep time did not differ between study nights (mean ± SD, 400 ± 20 min undisturbed, 396 ± 24 min fragmented; $p = 0.6$). Fragmentation decreased sleep latency on both the MSLT (11 ± 3, 7 ± 2 min; $p = 0.001$) and the MWT (34 ± 8, 24 ± 10 min; $p < 0.001$). Energetic arousal (22 ± 4, 19 ± 4; $p = 0.005$) and hedonic tone (29 ± 4, 27 ± 4; $p = 0.05$) decreased after fragmentation. Fragmentation impaired daytime function adjudged by the Trail-making B ($p = 0.05$) and PASAT 4-second tests ($p < 0.03$). One night of sleep fragmentation makes normal subjects sleepier during the day, impairs their subjective assessment of mood, and decreases mental flexibility and sustained attention.

**Safety Aspects of Local Endobronchial Allergen Challenge in Asthmatic Patients**—N Krug, LM Teran, AE Redington, C Gratziou, S Montefort, R Polosa, H Brewster, PH Howarth, ST Holgate, AJ Frew, MP Carroll. Am J Respir Crit Care Med 1996;153(4):1391.

Local endobronchial allergen challenge is being increasingly used to investigate the role of allergic inflammation in asthma. However, little information is available about the safety of this procedure and the changes induced in airway physiology. BAL and biopsy were performed at 10 minutes and at 4 to 6 hours, or 24 hours after segmental allergen challenge in 49 patients with atopic asthma. Two hours after challenge, FEV$_1$ was reduced from 97.6 ± 13.9 (mean ± SD) to 83.4 ± 21.7% predicted. FEV$_1$ remained reduced at 4 to 6 hours (87.7 ± 20.4%), but it had nearly returned to baseline by 24 hours (93.2 ± 14.0%). When endobronchial challenge was combined with BAL and biopsy, the initial fall in FEV$_1$ was slightly greater (from 101.8 ± 14.2 to 78.5 ± 13.6%). Bronchial responsiveness to methacholine was measured in 10 subjects, and it showed a twofold increase 24 hours after local challenge and lavage. Significant changes in FEV$_1$ and methacholine $PC_{20}$ were still detectable 72 hours after challenge. Widespread wheezing occurred in 29% of the subjects, but none of them had to be admitted to hospital. We conclude that local endobronchial allergen challenge, although producing measurable changes in airway physiology, is in general well tolerated and is an acceptable method to investigate airway pathophysiologic processes in patients with mild to moderate asthma.

**Aerosolized Cyclosporine in Lung Recipients with Refractory Chronic Rejection**—AT Iacono, RJ Keenan, SR Duncan, GC Smaldone, JH Dauber, IL Paradis, NP Ohori, WF Grgurich, GJ Burckart, A Zeevi, E Delgado, TG O'Riordan, MM Zendarsky, SA Yousem, BP Griffith. Am J Respir Crit Care Med 1996;153(4):1451.

This study evaluated aerosolized cyclosporine as rescue therapy for lung transplant recipients with unremitting chronic rejection. Nine patients with histologic active obliterative bronchiolitis and progressively worsening airway obstruction refractory to conventional immune suppression received aerosolized cyclosporine. Improvement in rejection histology was seen in 7 of 9 patients. We compared the changes in the FVC and FEV$_1$ over time using linear regression analysis in these 7 histologic responders and 9 historical control patients. During the pretreatment period for both the experimental and control groups, the FVC and FEV$_1$ declined at comparable rates. After aerosolized cyclosporine there was stabilization of pulmonary function, whereas in the controls there was continued decline. Cyclosporine blood levels were less than 50 ng/mL 24 hours after an aerosolized dose of 300 mg in 5 patients receiving oral tacrolimus. Nephrotoxicity, hepatotoxicity, and a greater than expected rate of infection were not observed. This study suggests that aerosolized cyclosporine is safe and may be effective therapy for refractory chronic rejection in lung transplant recipients.

**Testing for Human Immunodeficiency Virus Infection in Patients with Tuberculosis**—PF Barnes, C Silva, M Otaya. Am J Respir Crit Care Med 1996;153(4):1448.

To investigate the utility of testing all tuberculosis patients for HIV infection in Los Angeles, we prospectively evaluated 183 hospitalized patients with acid-fast smear-positive tuberculosis who gave no history of HIV infection. HIV serologic testing was performed, and the presence of risk factors for HIV infection was assessed by interview and review of the medical record. Thirty-three patients (18%) were infected with HIV. Based on data obtained by interview, 124 (68%) of 183 patients had at least 1 risk factor for HIV infection. The most common risk factors were re-

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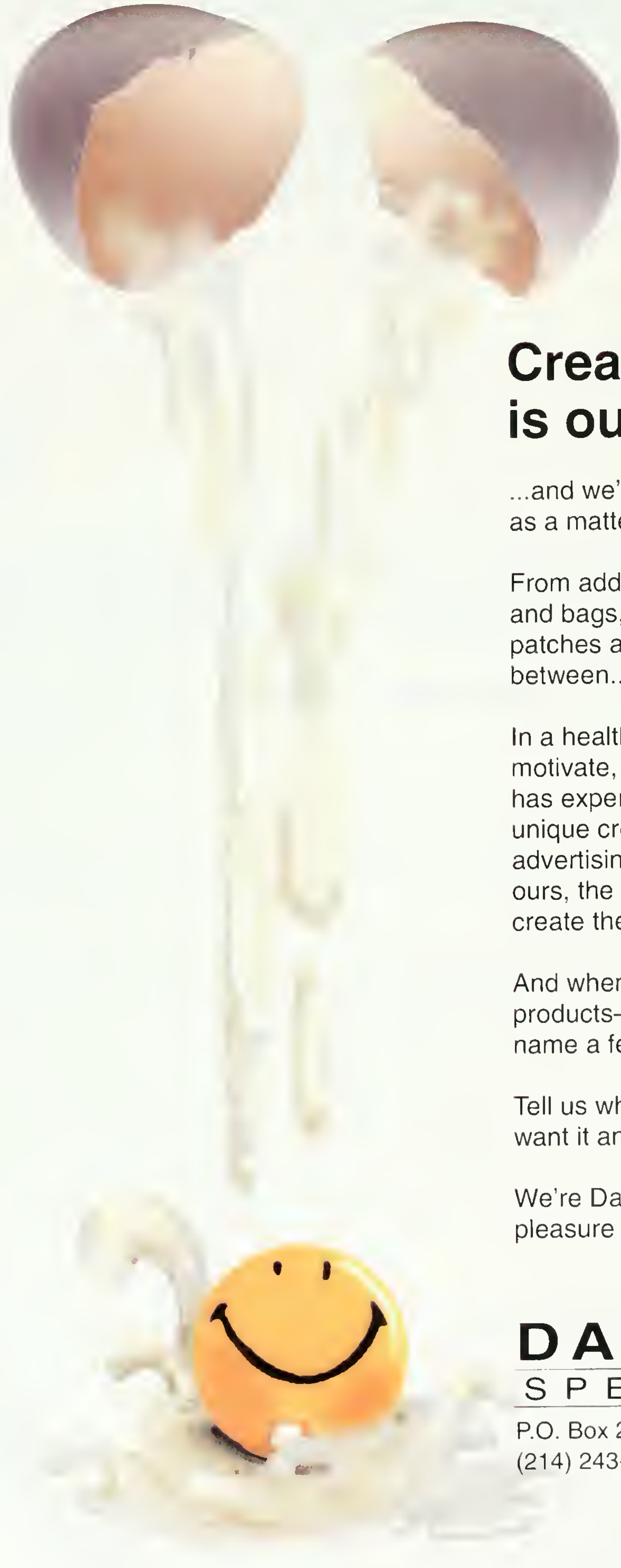

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lated to heterosexual transmission of HIV (prostitute contact, multiple sex partners, and a history of sexually transmitted disease). These risk factors were frequently not documented in the medical record. Among the 33 patients who were infected with HIV, 30 were identified by interviewing as having significant risk factors. We concluded that most tuberculosis patients in Los Angeles have risk factors for HIV infection and that systematic questioning does not identify risk factors in all HIV-infected tuberculosis patients. These data support current recommendations to screen all tuberculosis patients for HIV infection.

**Morbidity and Mortality in Children Associated with the Use of Tobacco Products by Other People**—JR DiFranza, RA Lew. Pediatrics 1996; 97(4):560.

OBJECTIVE: To evaluate the impact of adult tobacco use on the health of children. DESIGN: A literature review identified relevant research reports. Meta-analysis was used to compute a pooled risk ratio for each condition studied. The risk ratios were combined with data on exposure rates to produce estimates of the population-attributable risk. RESULTS: Each year, among American children, tobacco is associated with an estimated 284 to 360 deaths from lower respiratory tract illnesses and fires initiated by smoking materials, more than 300 fire-related injuries, 354,000 to 2.2 million episodes of otitis media, 5,200 to 165,000 tympanostomies, 14,000 to 21,000 tonsillectomies and/or adenoidectomies, 529,000 physician visits for asthma, 1.3 to 2 million visits for coughs, and in children younger than 5 years of age, 260,000 to 436,000 episodes of bronchitis and 115,000 to 190,000 episodes of pneumonia. CONCLUSIONS: The use of tobacco products by adults has an enormous adverse impact on the health of children. Although more research is needed in several areas, action to reduce the morbidity and mortality among children should not be delayed. New laws and policies are needed to grant children protection from bodily injury and death attributable to the use of tobacco products by others.

**Respiratory Characteristics during Sleep in Healthy Small-for-Gestational Age Newborns**—L Curzi-Dascalova, P Peirano, E Christova. Pediatrics 1996;97(4):554.

OBJECTIVE: Small-for-gestational age (SGA) infants born with intrauterine growth retardation (IUGR) differ from appropriate-for-gestational age (AGA) infants by: (a) alterations in a number of neurologic and neurophysiologic characteristics; (b) modified heart rate variability during the neonatal period; and (c) increased morbidity rates during the first months of life. However, there are no data on the impact of IUGR on respiratory function control at birth. METHODS: We studied 57 newborns who were 35 to 36, 37 to 38, and 39 to 41 weeks conceptional age (CA): 31 were AGA and 26 were SGA. All were clinically and neurologically normal at birth and none exhibited abnormal events during the first year of life. Polygraphic recordings were performed between 2 meals during the normal postnatal stay in the maternity ward. RESULTS: During both active sleep (AS) and quiet sleep (QS), SGA infants in all CA groups had significantly higher values for the incidence of 2 to 4.9 seconds and 5 to 9.9 seconds central respiratory pauses (RP), the apnea index (AI) [AI = % of nonbreathing time], and the time spent with periodic breathing (PB), as compared with AGA infants. Respiratory frequency was usually similar in SGA and AGA infants. In addition, the trend of age-related respiratory modifications was disturbed in SGA infants, as compared with AGA infants: at 39 to 41 weeks CA, SGA infants had no significant decreases in RP, AI, or PB, and no increase in respiratory frequency. However, between-state differences were similar in both groups. In all AGA and SGA infant groups respiratory frequency seemed to be an individual characteristic: infants who breathed faster during AS breathed faster during QS, and vice-versa. CONCLUSION. Our data demonstrate significant modifications in the establishment of respiratory rhythm control in SGA infants, whereas the patterns of state-related and subject-dependent breathing characteristics were similar in SGA and AGA infants. We speculate that the dysregulation of respiratory function control maturation observed in healthy SGA infants may be related to subtle brainstem modifications attributable to the decreased blood supply and chronic hypoxia associated with IUGR.

**Sweat Chloride Concentrations in Infants Homozygous or Heterozygous for $F_{508}$ Cystic Fibrosis**—PM Farrell, RE Koscik. Pediatrics 1996; 97(4):524.

OBJECTIVE: To determine whether an adequate volume of sweat could be obtained routinely from infants younger than 6 weeks old and to evaluate sweat chloride levels in infants with known genotype statuses, including heterozygote carriers for cystic fibrosis (CF). METHODOLOGY: Infants were evaluated using pilocarpine iontophoresis and measurement of sweat volume and chloride concentration. The majority of these infants were referred because of newborn screening test results positive for CF based on immunoreactive trypsinogen analysis. DNA analyses for the 3-base pair deletion at codon 508 of the CF transmembrane regulator gene ($F_{508}$ mutation) were performed whenever possible, and patients with CF were categorized by genotype. RESULTS: Sweat tests were performed successfully (≥ 50 mg of sweat) in 99.3% of the infants tested, and there was no difference in the proportion of unsuccessful tests in infants younger than or older than 6 weeks of age. The normal mean ± SD sweat chloride was 10.6 ± 5.2 mEq/L (95% confidence interval, 9.9-11.3). Patients with CF who are $F_{508}$ homozygotes or $F_{508}$ compound heterozygotes or who have 2 other non-$F_{508}$ mutant alleles were shown to have similar sweat chloride levels, with mean values of 99.9, 98.8, and 96.6 mEq/L, respectively. The group of infants who were found to be CF ($F_{508}$) heterozygote carriers, when compared with the healthy group, had mildly but significantly increased sweat chloride concentrations, with a mean ± SD of 14.9 ± 8.4 mEq/L (95% confidence interval, 13.4-16.4). CONCLUSIONS: Quantitative pilocarpine iontophoresis can be used successfully in infants younger than 6 weeks of age who are undergoing routine diagnostic evaluations to follow up newborn screening test results that are positive for CF. The upper limit of normal sweat chloride in infants should be revised to 40 mEq/L (mean ± 3 SD of the CF heterozygote carrier group). CF heterozygote carrier infants with 1 $F_{508}$ mutant allele show phenotypic manifestations of CF, including subclinical elevations of sweat chloride.

**The Efficacy of Nebulized Budesonide in Dexamethasone-Treated Outpatients with Croup**—TP Klassen, LK Watters, ME Feldman, T Sutcliffe, PC Rowe. Pediatrics 1996:97(4):463.

OBJECTIVE: To determine the added clinical benefit of nebulized budesonide in children with mild to moderate croup treated with 0.6 mg/kg oral dexamethasone. DESIGN. Randomized, double-blind, placebo-controlled trial. SETTING: Emergency department of a tertiary-care pediatric hospital with 47,000 visits/year. PARTICIPANTS: Children 3 months to 5 years of age with a syndrome consisting of hoarseness, inspiratory stridor, and barking cough and a croup score of 3 or greater after at least 15 minutes of mist therapy. Patients were excluded from the study if they had diagnoses of epiglottitis, chronic upper or lower airway disease (not including asthma), or severe croup or had received corticosteroids within the preceding 2 weeks. INTERVENTION: All patients received 0.6 mg/kg oral dexamethasone and were randomly assigned to receive 4 mL (2 mg) of budesonide solution (n = 25) or 4 mL of 0.9% saline solution (n = 25) by updraft nebulizer with a continuous flow of oxygen at 5 to 6 L/min. MAIN OUTCOME MEASURES: The primary outcome measure was the proportion of patients in each group who had clinically important changes (2 points) in the croup score during the 4 hours after treatment. RESULTS: Eighty-four percent (n = 21) of the patients who received budesonide had clinically important responses, compared with 56% (n = 14) in the placebo group. The number of patients who would need to be treated with nebulized budesonide for 1 patient to have a clinically important response is 4 patients. CONCLUSIONS: Despite receiving simultaneous oral dexamethasone, pediatric outpatients with mild to moderate croup have added, clinically important improvement in respiratory symptoms after treatment with budesonide.

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# MECHANICAL VENTILATION: VENTILATORY TECHNIQUES, PHARMACOLOGY, & PATIENT MANAGEMENT STRATEGIES

## Part II

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# High-Frequency Ventilation: A Ventilatory Technique that Merits Revisiting

Margaret S Herridge MD and Arthur S Slutsky MD

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**Types of HFV**
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## Introduction

Hooke[1] provided one of the earliest descriptions of artificial ventilation by demonstrating that an animal could be kept alive by using bellows to deliver gas to the lungs. Subsequent methods of ventilation have evolved to yield the positive pressure ventilators that are in use today. There is little doubt that the volume-cycled or pressure-limited modes of conventional mechanical ventilation (CMV) are effective in most patients. However, there is a subgroup of patients, with severe respiratory failure and intractable hypoxemia, who do not respond to conventional modes of ventilation. The ongoing frustration in managing these patients has provided the impetus for the development of alternative ventilatory techniques, such as high-frequency ventilation (HFV). A major goal in developing this method of ventilation has been to find a way to optimize gas exchange while minimizing ventilator-induced lung injury and the adverse hemodynamic consequences of high intrathoracic pressures. Early experiments in animals[2-4] showed that HFV was safe and provided adequate support of gas exchange at low lung pressures. In fact, a low airway pressure was believed to be the 'protective' mechanism offered by high-frequency ventilation and became the primary outcome variable in the largest randomized, controlled trial that had yet been conducted, evaluating high-frequency jet ventilation (HFJV), in adults.[5] The trial failed to show any advantage of HFJV over CMV. This is not surprising given recent literature on ventilator-induced lung injury demonstrating that a low-pressure strategy may result in worse lung damage as a consequence of repeated opening and closing of terminal airways.[6,7] Therefore, these data support the critical importance of an initial volume-recruitment maneuver so that lung inflation is optimal. The advantage of HFV, then, may lie with its ability to maintain alveolar recruitment while minimizing large, and potentially damaging, tidal pressure and volume excursions. The results of the larger clinical trials reported in the literature antedated the use of lung-volume-recruitment maneuvers.[5,8] Thus, the thesis of this paper is that many previous conclusions concerning the role of HFV in acute lung injury deserve revisiting.

## Types of HFV

It has been suggested that the term HFV be used to describe any type of mechanically assisted ventilation that

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employs reduced tidal volume ($V_T$) at an increased frequency.[9] Figure 1 illustrates the relationships of $V_T$ and frequency among the various devices used to support gas exchange.[10] The classification of the types of HFV is controversial because so many hybrids have evolved over a brief period of time. McCullough and colleagues[11] have proposed that different ventilators be categorized by their mechanism of expiration. HFV-passive (HFV-P) are those that rely solely on the passive recoil of chest wall and lung for expiratory flow, and HFV-active (HFV-A) are those that have active expiration. HFV-P devices include those used for high-frequency positive pressure ventilation (HFPPV) and HFJV. HFV-A devices include those used for high-frequency oscillatory ventilation (HFOV) and some high-frequency flow interrupters (HFFI). The simplicity of this classification system is appealing and may help make a complex and sometimes confusing body of literature more understandable.

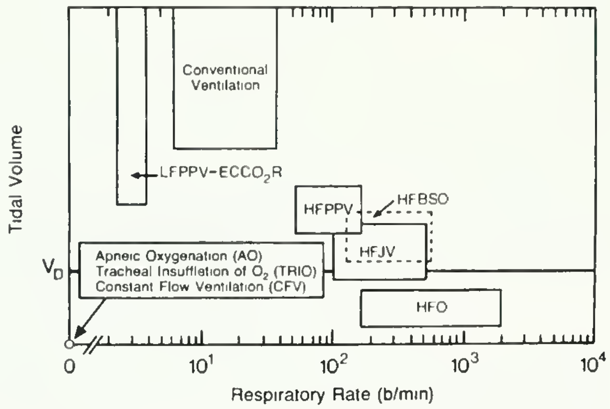
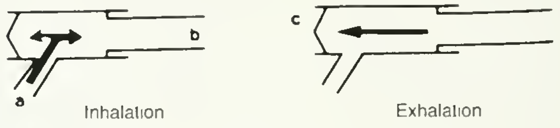


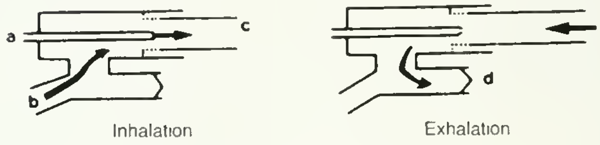
Fig. 1. The relationship of respiratory rate to dead space ($V_D$) and tidal volume among different alternatives to conventional mechanical ventilation for supporting gas exchange. The x-axis is a logarithmic scale and the y-axis is not quantitative. LFPPV-ECCO$_2$R = low-frequency positive pressure ventilation with extracorporeal carbon dioxide removal; HFPPV = high-frequency positive pressure ventilation; HFJV = high-frequency jet ventilation; HFBSO = high-frequency body-surface oscillation; HFO = high-frequency oscillation. (From Reference 10, with permission.)

## HFPPV

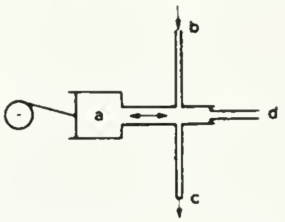
HFPPV was first developed by Öberg, Sjöstrand and colleagues in 1967.[12-14] The original rationale for this new mode of ventilation was to reduce dead space by endotracheal insufflation so that smaller $V_T$s and higher ventilatory frequencies could be used to provide adequate alveolar ventilation at lower mean airway pressure ($\overline{P}_{aw}$). Further, the inertia characteristics of the lungs during insufflation at high frequencies might avoid the adverse circulatory effects of mechanical ventilation. This method was developed during research on carotid-sinus reflexes and was used to minimize variations in blood pressure induced by tidal excursions.[12] The system delivered gas at high flows (175-250 L/min), and adequate gas exchange could be attained with $V_T$s of 3-4 mL/kg at 60-100 breaths/min. The reported advantages included decreased ventilator-patient asynchrony and reduced need for sedation.[15] HFPPV has been used primarily during laryngoscopy, bronchoscopy, and upper airway surgery.[16] A diagram of the HFPPV circuit is shown in Figure 2.[17]



High-Frequency Positive Pressure Ventilation



High-Frequency Jet Ventilation



High-Frequency Oscillation

Fig. 2. Gas-flow circuits of the three most common types of high-frequency ventilators. At the top of the figure is the circuit for high-frequency positive pressure ventilation. Note that flow enters from a low-compliance ventilator (a), is delivered to the lung without entrainment (b), and exits passively (c). The middle portion of the figure illustrates high-frequency jet ventilation. In this circuit, conditioned breathing gas (b) enters the lung through a small-lumen injecting cannula (c), entraining volume from adjacent reservoirs (b), and exits through a different path (d). Exhalation is passive. At the bottom is the circuit for high-frequency oscillation which relies on the to-and-fro motion of a piston (a). This application requires the use of a bias flow (b-c) that may be introduced anywhere along the inspiratory circuit. However, the closer the flow is to the lung, the more efficiently carbon dioxide is removed. (From Reference 17, with permission.)

## HFJV

HFJV evolved from a technique originally devised by Sanders[18] in which gas from a high pressure source is delivered through a small-bore cannula positioned in the airway. The opening and closing of a solenoid valve is regulated by a timer[19] or a fluidic control valve[20] and permits intermittent gas delivery. Because of the narrow outflow orifice, a jet effect is produced, entraining gas around the cannula (Fig. 2). Therefore, the total volume of gas received by the patient is the sum of the volume leaving the catheter and the volume of entrained gas. The ratio of inspiratory time to expiratory time (I:E) is usually in the range of 1:2 to 1:8, and respiratory rates in adults are commonly 100-200 breaths/min.[21] Precise $V_T$s are difficult to predict because they are a complex function of driving pressure, cannula resistance, inspiratory time, entrainment volume, and the back pressure, or impedance, generated by the respiratory system.[22,23] Similar to HFPPV, inspiration is active and expiratory flow is passive, driven by the passive recoil of the lung and chest wall.

The effect of the manipulation of different operating characteristics (eg, inspiratory time, driving pressure, frequency) varies, depending on the specific ventilator-endotracheal circuit that is used and on the patient's pulmonary mechanics.[24] However, some generalizations can be made. An increase in driving pressure produces an increase in $V_T$ that enhances $CO_2$ elimination.[25] This may be associated with an increase in end-expiratory lung volume, or functional residual capacity (FRC), and $\overline{P}_{aw}$, partially because of flow limitation during expiration. In contrast, increasing respiratory frequency or decreasing the I:E compromises $CO_2$ elimination because of the obligatory reduction in $V_T$.[26-28] Furthermore, increasing frequency above 100-150 breaths/min has been associated with significant gas trapping due, in part, to the specific mechanical properties of the patient's lung.[22]

## HFOV

HFOV is unique compared to other forms of HFV in that both inspiration and expiration are active—gas is actively pushed into the lung and actively withdrawn. Most oscillators employ an obligatory I:E of 1:1 because of their internal design and a wide frequency range (1 to 50 Hz, 1 Hz = 1 cycle/s). The ventilator itself does not supply fresh gas to the patient in the same way that conventional ventilators do. Rather, a fresh-gas bias flow is delivered to the circuit often from an external source (Fig. 2).[17,29-32]

### Mechanisms of $CO_2$ Elimination

HFV illustrates how effective $CO_2$ elimination can occur with small $V_T$s—often less than the volume of the anatomic dead space.[33] This is now (1996) a well-established concept, although initially it was felt to violate one of the fundamental tenets of pulmonary physiology—the requirement that $V_T$ be greater than the volume of the anatomic dead space. Of interest is that researchers had challenged this concept as early as 1915.[34,35] Gas transport during HFV probably results from several different mechanisms (Fig. 3), which have been reviewed in a number of papers.[17,36-44]

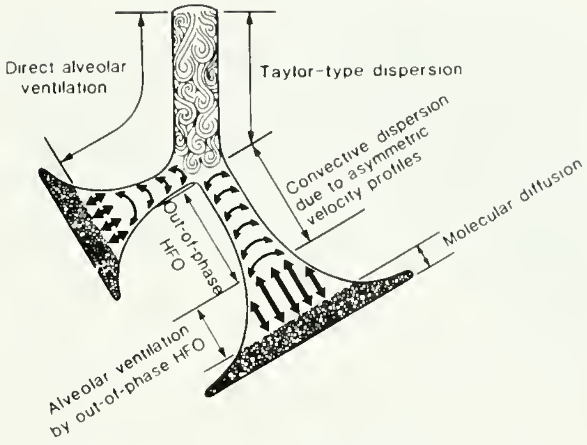

Direct alveolar ventilation
Taylor-type dispersion
Convective dispersion due to asymmetric velocity profiles
Out-of-phase HFO
Molecular diffusion
Alveolar ventilation by out-of-phase HFO

Fig. 3. Mechanisms of gas transport during high-frequency ventilation. These mechanisms are not mutually exclusive—more than one may operate in various regions of the lung at once, and they may be synergistic. Alveolar ventilation by out-of-phase HFO is also known as pendelluft. (From Reference 38, with permission.)

### Bulk Convection

During normal tidal breathing, inspired air passes directly to the gas exchanging regions of the lung by bulk convection. Even when the $V_T$ is reduced to a level that is less than the anatomic dead space, there will be some direct alveolar ventilation. This is related not only to the proximity of some alveoli but to asymmetries of the lung and nonuniformity of the flow-velocity profiles in the conducting airways.[36,38]

### Asymmetric Velocity Profiles

This mechanism was first proposed by Haselton and Scherer.[39-41] With an oscillatory flow, there are differences in velocity profiles depending on flow direction. Over the course of several oscillation cycles, gas particles move forward or backward depending on whether they reside in the center or near the wall of the airway lumen. Therefore, at the end of each oscillation cycle there is a net bidirectional flow. As fresh gas is introduced, radial diffusion occurs in response to local gas pressure differences, and, because of this bidirectional flow, oxygen-rich gas is delivered distally while carbon-dioxide-rich gas moves proximally.

### Pendelluft

At high respiratory frequencies the distribution of gas depends on time-constant ($\tau$) inequalities. Gas flows from 'fast' lung regions (those with short $\tau$) to 'slow' lung regions (those with long $\tau$) to achieve a back-and-forth 'sloshing' motion, which has been termed pendelluft—German, for 'air swing.' This leads to mixing and eventual homogenization of regional gas concentrations. This principle was borne out by Lehr and colleagues[45] who were able to demonstrate differences in the sequence of expansion within and between lung lobes, suggesting that gas did indeed circulate among different lung regions. Further, Allen et al[46] and Fredberg and co-workers[47] showed that phase differences in pressure were not uniformly distributed. These phase differences could establish circulating currents that facilitated alveolar gas interchange several times within the time period normally required to clear the lung once.

### Taylor Dispersion

Taylor[48] demonstrated that the addition of convective flow to a diffusive process significantly increases dispersion of tracer molecules. Fredberg[49] proposed that Taylor dispersion in turbulent flow was the main mechanism of gas transport in HFV. Based on this theory, he hypothesized that $CO_2$ elimination would be proportional to the product of the $V_T$ and respiratory frequency. Subsequent work has shown that $V_T$ is a greater determinant of gas exchange than frequency during HFV, thus supporting the contention that multiple mechanisms contribute to $CO_2$ elimination during HFV.[31] A number of experimental studies evaluating gas transport mechanisms have shown that $CO_2$ transport varies as the product of frequency and $V_T$ raised to a power between 1 and 2.[31,32,47]

### Cardiogenic Mixing

Slutsky[50] proposed that gas mixing in HFV could be enhanced by cardiogenic oscillations. Thus, the continuous pumping motion of the heart acts to potentiate peripheral gas mixing and enhance distribution. Similarly, the gas transport mechanisms thought to be operative during HFV could explain gas mixing by cardiogenic oscillations.

### Molecular Diffusion

Molecular diffusion plays a central role in gas transport in the terminal airways. However, the residence time within the alveolar region is markedly reduced during HFV and, therefore, the time available for equilibration within a particular cycle is reduced.

## Mechanisms of Oxygenation

The efficiency of gas exchange conferred by HFV is inextricably linked to the nature of the $O_2$ and $CO_2$ dissociation curves. Because the $CO_2$ dissociation curve is relatively linear throughout the physiologic range, one can achieve normocapnia through hyperventilation even when a substantial proportion of alveoli are underventilated or nonventilated. However, the $O_2$ dissociation curve is quite alinear and, therefore, dictates that no degree of hyperventilation can compensate directly for an abnormal relationship of ventilation to perfusion ($\dot{V}$-$\dot{Q}$ mismatch). Therefore, HFV can be used to treat patients with generalized alveolar hypoventilation, as with a bronchopleural fistula.

The principles of oxygenation during HFV are similar to those operative during CMV. To improve oxygenation, HFV must be coupled with an optimal lung-volume/alveolar-recruitment strategy. Such a recruitment strategy helps to overcome alveolar opening pressure and raises tidal ventilation to the more favorable, linear portion of the volume-pressure relationship. The utility of HFV may be its ability to maintain end-expiratory lung volume while minimizing peak alveolar stretch, thereby minimizing ventilator-associated lung damage.[6,11]

## Purported Advantages of HFV

Nonconventional modes of ventilation were devised in an attempt to address historical concerns with conventional mechanical ventilation. New systems were developed to (1) minimize the detrimental impact of intrathoracic pressure variations on cardiovascular function; (2) facilitate a motionless field for certain surgical procedures; (3) improve gas exchange in patients for whom CMV is ineffective; and (4) minimize ventilator-induced lung injury. The advocates of HFV proposed that the use of small $V_T$s would decrease alveolar pressure swings and minimize the risk of barotrauma. The success of HFV in fulfilling these goals has been somewhat mixed. However, there is little doubt that it is effective in certain endoscopic and surgical procedures, and it improves ventilation in certain clinical situations; although, like CMV, in the absence of optimal lung recruitment, HFV is unable to benefit oxygenation.

Despite early optimism that HFV would minimize hemodynamic compromise, no compelling data support that it is truly cardiac sparing when compared to CMV at equivalent $\overline{P}_{aw}$.[4,51] Perhaps the greatest advantage of HFV lies in its ability to support gas exchange while minimizing ventilator-induced lung injury. Early animal data in two models of acute lung injury demonstrated that HFV, when combined with a sustained inflation, can result in larger mean lung volumes and improved oxygenation compared with CMV.[52,53] Further data not only confirmed that HFV in combination with volume recruitment provided good gas exchange but also demonstrated histologic evidence of decreased lung injury compared with CMV. During a 5-hour period of ventilation, all CMV animals developed diffuse hyaline membranes, whereas there was no evidence of lung damage in the HFV group.[53] A later study showed that maintenance of alveolar volume is the key mechanism in the prevention of ventilator-induced lung injury and that alveoli must be actively re-expanded and then kept expanded with whatever $\overline{P}_{aw}$ is required.[11] Therefore, volume recruitment is critical to maintain the patency of terminal airways, decrease large pressure-volume excursions, and minimize pressure-induced lung injury. Early clinical trials did not support the observations made in these animal models. However, their ventilation strategies involved minimizing pressure, believing that would minimize pressure-induced lung injury. This practice may have confounded their conclusions. Of interest, a recently published clinical trial[54] in pediatric patients with acute respiratory distress syndrome (ARDS) compared HFOV and CMV. These investigators incorporated an aggressive volume-recruitment protocol and their results support the observations made in these animal studies. Earlier, Clark et al[55] studied 3 groups of neonatal patients with respiratory failure. One group received CMV alone, another received CMV and HFOV, and a third group received HFOV alone. The incidence of chronic lung disease in the infants who were treated with HFOV alone was significantly lower than in the infants treated with CMV alone. These investigators applied an aggressive lung-volume-recruitment strategy with the use of HFOV.

Some of the problems clinicians once had applying HFV may have been related to their lack of a theoretical understanding of how to select the appropriate ventilator settings to minimize lung injury. Venegas and Fredberg[56] proposed guidelines for the rational selection of frequency, $V_T$, and $\overline{P}_{aw}$ during HFV. Apart from pure molecular diffusion, gas transport in the airways depends largely on convective fluid motion. Their analysis was based on two aspects of fluid motion: (1) the transport aspect in which gas is driven by convective fluid motion and (2) the mechanics aspect in which convective fluid motion is driven by pressure differences imposed by the chest wall or the ventilator. The goal, then, is to achieve adequate gas transport by applying distending pressures that minimize alveolar collapse and injury. These authors addressed the problem of achieving adequate alveolar ventilation at minimal pressure cost by dividing it into two problems: (1) determination of the pressure cost per unit of convective oscillatory flow and (2) determination of the convective flow cost to achieve a unit of alveolar ventilation. They used models of gas exchange and lung mechanics to subsequently determine the total pressure cost of HFV as a function of both the ventilator settings and the physiologic variables of the patient. Their analysis supported the importance of using HFV in infant respiratory distress syndrome and of the use of optimal levels of positive end-expiratory pressure (PEEP). Further, it underscored the danger of lung injury to the collapsed, or derecruited, lung.[56]

## Problems with HFV

A major difference between HFV and CMV is the requirement for much greater flows to achieve normocapnia. Because of this, there is a greater potential for gas trapping related to airflow limitation during exhalation.[57-59] Gas trapping is particularly worrisome in patients whose respiratory systems are highly compliant or who are being ventilated using prolonged I:Es, and it is important to have some ongoing means of detecting alveolar hyperinflation—the relationship of alveolar pressure ($P_{alv}$) to proximal $\overline{P}_{aw}$. This relationship can be measured by simultaneous occlusion of the airway with cessation of inspiratory flow and determination of the equilibrium pressure, which represents $P_{alv}$. When there is no gas trapping, this equilibrium pressure is not higher than the proximal $\overline{P}_{aw}$.[60,61]

Necrotizing tracheobronchitis (NTB) has been reported in animals and in patients ventilated with HFV[62-64] and is believed to be due, in part, to inadequate humidification of the high-velocity gas flow.[65-67] Although some animal studies have shown that humidification of only the entrained gas is sufficient, vigilance is required to avoid mucosal drying and its potentially devastating repercussions. With current systems, NTB has ceased to be a serious problem.

## Clinical Studies in HFV

### HFJV

HFJV has some clinical role for ventilating patients during certain special procedures and for those with established barotrauma. Its role in the management of acute lung injury remains less clear. No compelling clinical data support the superiority of HFV over CMV. However, given the evolution in our understanding of the mechanisms that initiate and perpetuate lung injury, the early studies may have been flawed.

**HFJV during Procedures.** HFJV has been used satisfactorily during bronchoscopy, laryngoscopy and tracheal surgery.[68-71] It offers the advantage of adequate $V_T$s without a gas-tight system and can be an effective ventilatory strategy when there is competition for access to the airway.[21] It imparts a particular advantage in its ability to provide a near-motionless surgical field, such as during laser resection of endobronchial tumors[72] and during pediatric and adult cardiovascular procedures.[73-75]

**HFJV for Bronchopleural Fistulae.** Early enthusiasm for HFJV came from the observation that it was able to support gas exchange in patients with bronchopleural fistulae (BPF) in whom air leaks had prevented adequate alveolar ventilation.[19,66,76] The purported advantage of HFJV was its ability to provide adequate alveolar ventilation at lower peak and mean tracheal pressures than CMV, thereby permitting resolution of the air leak. Because, at high-frequencies, the distribution of ventilation becomes less dependent on regional resistance-compliance and more on regional resistance-inertance of the airways, HFJV might offer an advantage in the treatment of BPF. Unfortunately, when substantial venous admixture or ventilation-perfusion mismatch is present, HFV offers little benefit over CMV.

The use of HFJV in BPF has not been rigorously studied. This is understandable given that BPF is often life-threatening. However, despite unproven efficacy, a trial of HFJV remains worthwhile when CMV has failed because it can support ventilation using lower airway-pressure swings and may temporize in a clinical emergency.

**Acute Lung Injury.** That mechanical ventilation can induce and/or potentiate lung injury has been known since the advent of positive pressure ventilation. Greenfield and colleagues[77] were the first to demonstrate that dogs ventilated for 1-2 hours with peak airway pressures of 28-32 cm $H_2O$ developed increased surface tension and significant atelectasis. Barsch et al[78] and Kolobow et al[79] confirmed these observations and provided histologic evidence of vascular injury, alveolar edema/hemorrhage, and hyaline membrane formation in affected animals. In addition to high peak airway pressures, ventilation with high $V_T$s has also been described as an independent contributor to lung injury.[80-82] Of interest, several authors have shown that the use of PEEP ameliorates lung injury.[82,83] Enhorning[84] and Robertson[85] postulated that acute lung injury in the atelectasis-prone lung arose from shear stress associated with repeated opening and closing of terminal airways. As previously discussed, Bryan, Froese and colleagues[11,52,53] further supported this hypothesis by showing that HFOV, following volume-recruitment maneuvers (ie, inflation above the opening pressure of the lung), markedly diminished acute lung injury. Sandhar and co-workers[86] reached similar conclusions using PEEP to prevent alveolar collapse during CMV in a surfactant-deficient rabbit model of infant respiratory distress syndrome. Recently, Muscedere and co-workers[7] demonstrated that ventilation at low end-expiratory lung volumes potentiates lung injury and is as detrimental as overdistention. Similar findings have been reported by Cordero et al.[87,88] The ability of PEEP to recruit and maintain alveoli above the lower inflection point—ie, the opening pressure of the lung—minimizes shear stress and may account for its protective role in ventilation of the acutely injured lung.[7]

Although these data provide compelling evidence for the protective effects of adequate lung volume on the acutely injured lung, implementing and regulating a volume-recruitment strategy during HFJV is difficult. The optimism of the early investigators that HFJV could offer a means of minimizing the lung injury that is associated with ventilator therapy has not been confirmed. Several prospective studies have failed to demonstrate any substantive advantage of HFJV over CMV.[89,90] The largest prospective randomized evaluation of HFJV was published in 1983.[5] HFJV was shown to be as effective as, but not superior to, CMV in maintaining oxygenation and ventilation in patients with ARDS, and no difference in mortality was found between the groups.

At that time, the use of low ventilating pressures was believed to minimize lung injury and, therefore, no attempt at volume recruitment was made. It is not surprising, then, that these clinical studies failed to show any significant improvement in oxygenation with HFJV. However, since that time, several studies have demonstrated that oxygenation is largely influenced by mean transrespiratory pressure in the atelectasis-prone lung.[22,90,91] Thus, it follows that if lower airway pressures are the clinical goal, oxygenation may be compromised and lung injury worsened.

Additional work has shown that oxygenation is also dependent on the maintenance of lung volume.[11,33,48,49] It is not unexpected that, up to a point, the amount of lung volume that is recruited is proportional to the pressure applied during a sustained inflation. The goal, following volume recruitment, is to maintain a pressure above the closing pressure of the recruited alveoli.[11] Some authors have suggested a method of determining the window between opening pressure and closing pressure.[6] This involves imposing an arbitrary, but safe, increase in airway pressure for a 10-second period to determine whether a sustained rise in $P_{aO_2}$ results. If this maneuver has the hoped-for effect, this new pressure is believed to be above the closing pressure of the lung. Using this technique may assist the clinician in achieving optimal lung-volume recruitment without the risk of overdistention. In the above-mentioned clinical trials,[89,90] no such strategy was used.

Maintenance of lung volume is also important in minimizing ventilator-induced lung injury. As previously discussed, animal studies suggest that ventilation at lung volumes below the lower inflection point of the respiratory system may potentiate lung injury through the repeated small-airway opening and closing that can occur during the respiratory cycle.[7,87,88] Thus, the use of a low-pressure/low-volume strategy in these HFJV studies may have inadvertently resulted in more lung injury than might have occurred with CMV.

Histologic and physiologic data from animal experiments support the rapid development of ventilator-induced lung injury.[73-75] Therefore, any important advantage conferred by HFV could only be realized if countermaneuvers were instituted early in the evolution of the injury. In most early clinical reports, HFV was employed as a salvage regimen—in patients at high risk of imminent death—and, clearly, was not evaluated under optimal circumstances—an important consideration when evaluating this evidence.

## HFOV

Much of the clinical data for HFOV is found in the pediatric literature. Whereas, several investigators demonstrated in early trials that HFOV could support gas exchange and often could result in a decreased $F_{IO_2}$, others found few advantages over CMV.[30,92,93] A large, multicenter, randomized, NIH-sponsored clinical trial was conducted to compare the safety and efficacy of HFOV with CMV in the treatment of respiratory failure in preterm infants. HFOV was shown to be safe and effective but did not decrease the incidence of chronic lung disease or confer any survival advantage. In fact, it was found to be associated with an increased incidence of pneumoperitoneum, intracranial hemorrhage, and periventricular leukomalacia.[8] However, the strategy employed was a conservative one, including sighs limited to one second and the same $\overline{P}_{aw}$ in both groups. Previous animal data have suggested that longer sighs and higher $\overline{P}_{aw}$ are needed to recruit the lung and that this strategy results in significantly less lung injury.[37,48,49,91] This explanation may account for these disappointing results, particularly because other investigators have reported both intermediate and long-term benefit in infants treated with HFOV.[51,94,95]

A recent prospective, randomized comparison of HFOV and CMV in pediatric respiratory failure employed an aggressive volume-recruitment strategy.[54] The optimal lung volume strategy was associated with a higher $\overline{P}_{aw}$ in the HFOV group, but with a lower frequency of air leaks. This conclusion was supported by a decreased need for supplemental oxygen at 30 days and overall improved outcome compared to CMV. These data support the conclusions drawn from animal studies[96,97] and are very promising.

### HFPPV

Data on the use of HFPPV in clinical practice are limited. It has been used with success in endoscopy and laryngeal surgery where it is convenient to ventilate patients through a small catheter.[13,15,98,99] However, in adult and pediatric patients with acute lung injury, HFPPV showed no advantage over CMV when oxygenation and cardiac output were used as clinical end points.[100,101]

## Cardiac Effects of HFV

In theory, HFV could augment cardiac output because the frequencies used in adults are similar to the range of heart rates. Methods were devised to synchronize inspiration with the electrocardiogram.[102,103] Isolated reports and small series support the cardiac-sparing effect of HFJV.[104,105] However, no definitive evidence that HFJV improves hemodynamic tolerance over CMV has been found. Both animal and human studies in HFV and CMV have shown equivalent decreases in venous return and elevation in right ventricular afterload when equivalent $\overline{P}_{aw}$s are applied.[106,107] In anesthetized dogs, Gotshall et al[108] observed a reduction in stroke volume and arterial and pulmonary blood pressures when the frequency of HFJV approached the heart rate.

## In Summary

HFV is a safe and viable mode of ventilation that effectively facilitates $CO_2$ elimination and supports oxygenation. It may be particularly useful in providing a near-motionless field during endoscopy and certain surgical procedures. Evidence for its potential as a means of improving oxygenation and minimizing ventilator-induced damage in the acutely lung-injured patient is sparse. However, we argue that any advantage that may be present could not have been demonstrated given the strategies employed and the clinical end points and study designs of the larger randomized, prospective trials.

Our understanding of the variables that independently contribute to ventilator-induced lung damage is evolving. Increasing evidence supports that ventilating patients at a lung volume low enough to allow the lung to collapse is as deleterious as using excessively large lung volumes with its risk of overdistention. The best clinical strategy, then, involves aggressive volume recruitment followed by the use of one of several ventilatory strategies to maintain this optimal lung volume. Thus, the primary goal is a physiologic one and many different modes of mechanical ventilation are able to achieve it.

HFV may decrease the risk of lung injury by limiting the magnitude of pressure/volume excursions, but it may not be uniquely qualified in this regard. Rather, it may be argued that HFV is one of several, equally viable ventilatory techniques able to protect the lung from iatrogenic harm. HFV should not be discarded because it has failed to show an overwhelming advantage over other modes of ventilation. Instead, it should be welcomed as an addition to the repertoire of ventilatory options available to the clinician who cares for patients with respiratory failure and intractable hypoxemia.

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## Slutsky Discussion

**Kacmarek:** Every time I listen to somebody talk about high-frequency ventilation, I get confused again. Theoretically, it appears to me that this should be the greatest thing that is out there. It does everything right—we're above the low inflection point; we're below the high inflection point. Yet, whenever I look at the pediatric literature that seems to imply that high frequency is better,[1,2] I'm disappointed because the protocols used for conventional ventilation don't always follow the same approach to maintaining high lung volume and minimizing a peak airway pressure. When we look at the adult literature[3,4] and examine the approaches that were used in the conventional arm of the study to ventilate patients, we find approaches that today are considered disastrous. Yet, the results are comparable—no difference between high-frequency approaches and conventional approaches. Is there really a role for high-frequency ventilation; do you believe there is a significant difference between high-frequency and conventional ventilation; and are we missing the boat by not using this more in the adult population?

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**Slutsky:** Bob, you have asked a complicated question. I don't think we are missing the boat yet. My view is you have to have data in the literature to support the use of a technique in patients. At present, I don't think the data are sufficiently strong for advocating high-frequency ventilation in all adult patients. However, I concur with you in the sense that when you look at the putative advantages, they look tremendous. When you look at the animal studies, they look tremendous. I think the problem has been that when this technique has been applied—certainly in early studies—investigators didn't really understand the basic mechanisms by which a mechanical ventilator caused damage to the lung and, hence, didn't understand the optimal way to apply high-frequency ventilation. I think the feeling was that if you used smaller tidal volumes, that in and of itself would be beneficial. That's not really the issue. The issue, I think, relates not so much to the dynamics during high-frequency ventilation but to the statics. By the statics, I mean where are you on the pressure-volume curve? Have you recruited the lung, and are you ensuring that it doesn't derecruit? That's really what's important. That approach wasn't applied in most studies. The second issue is that conventional ventilation is continually changing—we're minimizing tidal volumes and end-expiratory pressures. In many ways, we're using a strategy similar to high-frequency ventilation. Thus, you may obfuscate any difference between the two. It's like trying to compare a low-tidal-volume ventilation strategy with conventional ventilation, while conventional ventilation is changing all the time because of all the papers on limiting peak pressures. So, there's going to be overlap. You may have trouble finding a difference between the two. That's because everything is changing.

**Kacmarek:** That is exactly my interpretation of the data. When I hear somebody present this, I always feel bad that we never use it clinically. Do you ever use high-frequency ventilation?

**Slutsky:** We do use it, but very infrequently—only a few times a year. We use it more as a salvage, quite frankly. It's just because to do this right, you have to set up a trial, and we're doing other trials. Quite frankly, in many ways this is not the best way to use HFV. The animal evidence clearly indicates that you should be using techniques like this or applying any of the strategies *very early*. If you try to apply the strategy after a few days of ventilation during which you injure the lung, you're not going to find much of an effect. You just have to look at the histology—it's dramatic. There are hyaline membranes; there's this denudation of the epithelium—pieces of the epithelium lying in the airway. It's going to take a long time for that to heal. So if you really want to *prevent* the injury, you don't want to wait until the patient has rip-roaring lung injury and say "Well, now's the time to use this interesting ventilatory strategy." Whether it be high-frequency or whether it be a pressure-limited strategy, I think you want to apply whatever strategy you choose as early as possible to prevent injury.

**Branson:** One of the things we alluded to at the end of Bill's (Peruzzi) talk was that PEEP seems to have a protective effect against lung injury. That's something I tried to get Dave Pierson to admit in our video conference, and he never would—I think because of his whole idea about using the lowest PEEP possible. But in one of the studies that you showed, the study by Hamilton et al,[1] when they were using CMV, they were using no PEEP. Then they compare it to high frequency, which, of course, provides PEEP innately, by the way it functions. We shouldn't lose sight of the fact that when you're using high-frequency ventilation, you really are establishing end-expiratory lung volume and ventilating through it, which I think is what you were saying at the end. This whole concept of early—I hate to say aggressive—application of PEEP in the 10-15 cm range seems to be a key in preventing ventilator-induced lung injury.

1. Hamilton PP, Onayemi A, Smyth JA, Gillan JE, Cutz E, Froese AB, Bryan AC. Comparison of conventional and high-frequency ventilation: oxygenation and lung pathology. J Appl Physiol 1983;55(1 Part 1):131-138.

**Slutsky:** Certainly, the major difficulty is that it is very difficult to perform the appropriate studies in humans. However, there is one study by Amato and colleagues[1] from Brazil in which they used a strategy of limiting high pressures but also applied sufficient PEEP, greater than the inflection point. They found significant differences in a number of important variables but not in mortality. They've continued the study, and I think they're up to about 50 or 60 patients. They've now showed a difference in mortality between the conventional group and this group that limits the high pressures and uses substantial PEEP. Whether it's the high PEEP that is important or whether it's limiting the high pressure, we don't know. A number of other ongoing studies are comparing conventional mechanical ventilation to a strategy in which peak pressures are minimized, so maybe we'll be able to sort out this issue to some extent.

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**Hess:** Could you say a few words about the use of high-frequency ventilation with bronchopleural fistula? That's where it's still discussed sometimes at the bedside. When I'm asked if we should consider using high-frequency ventilation for someone who has a big air leak, I go through my anecdotal experience (where it really hasn't seemed to work very well). A couple of papers out there tend to indicate that maybe it doesn't work very well.

**Slutsky:** I think the answer is quite likely summarized in your question. A couple of early papers suggested that HFV was beneficial in patients with bronchopulmonary fistula; a couple of recent papers suggested that there's not much use. I think that the underlying rationale is interesting—at low frequencies, the distribution of ventilation is determined by the product of the local resistance and compliance (RC, or time constant)—with bronchopulmonary-cutaneous fistula, the compliance is that of the room. Therefore, much of the volume during conventional ventilation leaves through the fistula. At high frequencies, the relevant variable is the resistance and, thus, theoretically one can redistribute flow—perhaps, away from the fistula. Having said all of this—given the data or lack thereof—I think that it is reasonable when other options are unsuccessful.

**Hess:** One of the things that I always get back to in that discussion—which is one of the points that you made—is that if we haven't done this in the last 10 years, and this patient has this big air leak and is not doing well otherwise, is this the patient in whom we want to do it for the first time in 10 years?

**Slutsky:** I think that's a very important point. Although in my particular hospital, we use HFV infrequently, we have a close relationship with the hospitals across the street, so that among us, there is sufficient experience to feel comfortable with it. Possibly the most important factor in applying any new mode of ventilation is the staff's familiarity with it.

**Kacmarek:** I just wanted to follow-up on the discussion regarding the use of PEEP and lung injury. My question is, If all that you say is true (and I agree with the data), should we be using 10 cm $H_2O$ PEEP on every patient? We started by limiting high airway pressure in all patients. We rarely exceed 35 cm $H_2O$ plateau pressure. We ventilate most patients with pressure much lower than 35 cm $H_2O$. But in the average patient we rarely set PEEP at a level equivalent to the inflection point unless we have some indication that there is acute lung injury and we need to deal with oxygenation. From what you said, injury occurs rapidly in animals if the PEEP is below the inflection point. When we ventilate patients should we be using much higher PEEP than is customarily used in the average patient without acute lung injury, to minimize the risk of ventilator-induced injury?

**Slutsky:** That's a very good question, Bob. Unfortunately I cannot give you a definitive answer. First of all, given the animal literature, it's a tenable hypothesis that should be tested. However, I don't think it should be used on *all* patients. I think people who are at high risk for developing acute lung injury (ALI) or certainly have ALI, it probably would make sense to use a reasonable PEEP early on. Unfortunately, the only human data using PEEPs that high in a good study are the data of Amato that I quoted earlier. However, this was only one study, and they also limited peak pressures, so it's uncertain which particular components of the ventilatory strategy were critical.

**MacIntyre:** Bob, we have been looking at this carefully in devising the ventilator strategy for the NIH ARDS network trial. You imply that inflection points are always going to be up in the 10-15 cm $H_2O$ or more range. In fact, I think there's quite a range of inflection points. In the study by Laurent Brochard and his group (unfortunately, he isn't here yet),[1] the average, I think, was 10 cm $H_2O$ but 2 standard deviations was about 6, so it ranged anywhere from about 4 up to about 16. So, I'm not so sure that current practice is grossly out of the inflection-point range. We may actually be doing it already, to a certain extent, in most patients. I guess my question, then, goes back to Bill's (Peruzzi) stuff and what I'm going to talk about this afternoon. Is gas exchange, as Bill suggested, a reasonable surrogate marker, if you will, for being at an appropriate place in the pressure-volume curve, or do we have to make these measurements?

1. Roupie E, Dambrosio M, Servillo G, Mentec H, El Atrous S, Beydon L, et al. Titration of tidal volume and induced hypercapnia in acute respiratory distress syndrome. Am J Respir Crit Care Med 1995;152(1):121-128.

**Slutsky:** First of all there are no answers, obviously, or else your group would have come up with an answer. So, there aren't sufficient data in the literature to guide us on this issue. The range of inflection points varies, and in that Amato paper the inflection point ranged from 6-20 cm $H_2O$ for their 28 patients. So, it's quite large. Bob's (Kacmarek) question was a practical one. Clearly, if you can measure mechanics in everybody, that's what you probably should do. I'm not sure that's practical in every day practice. The use of oxygenation as a surrogate makes sense physiologically, but at present there is a paucity of human data to rely on.

**MacIntyre:** You made the comment that if you can inflate the lung, to say 20-25 cm $H_2O$, which would be equivalent to a normal TLC, that, in fact, the inflection point you're worried about on the deflation limb is actually going to be considerably less. So, in fact, aiming for Brochard's average[1] of 10 or Amato's 10 to 12[2] may be too high. Perhaps moving back down closer to 5 or 7 or 8, which is kind of standard practice, may be doing OK.

1. Roupie E, Dambrosio M, Servillo G, Mentec H, El Atrous S, Beydon L, et al. Titration of tidal volume and induced hypercapnia in acute respiratory distress syndrome. Am J Respir Crit Care Med 1995;152(1):121-128.
2. Amato MBP, Barbas CSV, Medeiros DM, Schettino G deP P, Filho GL, Kairalla RA, et al. Beneficial effects of the "open lung approach" with low distending pressures in acute respiratory distress syndrome: a prospective randomized study on mechanical ventilation. Am J Respir Crit Care Med 1995;152(6):1835-1846.

**Slutsky:** Let me answer the two parts of your questions from before, as well. One relates to oxygenation, and I want to bring up another point in terms of the timing. I think, in terms of oxygenation, it probably is a reasonable approach. I'm not sure exactly how to do it. Allison Froese and her group have done some studies in humans.[1] She uses oxygenation as a surrogate for keeping the lung open. That's a reasonable approach. One approach I've been thinking about is to inflate the lung, go to TLC, come down on the deflation limb—pick a number: 12, 10 cm $H_2O$ and monitor oxygenation over a little period of time. When oxygenation is stable, drop the PEEP a little bit, and repeat the oxygenation measurements. When the oxygenation goes off, you may be at the inflection point on the deflation limb. Really, it probably tells you the same thing as the pulmonary mechanics—the lung is open and you get better oxygenation. That brings up the second point, that one reason these approaches of high PEEP are extremely successful in animal studies is because you really have acute lung injury. You produce the injuries, and you're right there at that instant in time to use whatever ventilatory strategy you've decided on. As you know, there are a few phases to ARDS, and it's probably in that first couple of days where there is an inflection point and there is recruitable lung. If you look later on, the amount of lung that's recruitable has decreased. Probably, using high PEEP and other recruitment strategies are not going to help at all and may be detrimental. So, timing is important—where you are in the phase of your ARDS. In other words, if you get a patient from another hospital who has been on low PEEPs for > 96 hours and is doing poorly, I think you should treat that patient very differently from someone who has sustained trauma and comes to you soon after the injury. There's nothing to recruit if there's only fibrotic lung—using recruitment strategies on a fibrotic lung may be detrimental.

1. Froese AB, Butler PO, Fletcher WA, Byford LJ. High-frequency oscillatory ventilation in premature infants with respiratory failure: a preliminary report. Anesth Analg 1987;66(9):814-824.

# Exogenous Surfactant Therapy: An Update

Carl F Haas MLS RRT and John G Weg MD

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## Introduction

Patients with abnormal pulmonary gas exchange and altered respiratory mechanics often require medical intervention to improve the efficiency of breathing. Treatment usually consists of a combination of mechanical (eg, incentive spirometry, positive pressure breathing), positional (eg, prone vs supine, postural drainage), and pharmacologic (eg, oxygen, bronchodilator, steroid, antibiotic) therapies. One of the most recently available pharmacologic agents is exogenous surfactant.

In this paper, we review how the normal, endogenous surfactant system functions, how surfactant is involved in the respiratory distress syndrome (RDS) of the neonate and the acute respiratory distress syndrome (ARDS) of the adult, and the role of exogenous surfactant as therapy for these two syndromes.

## Review of the Normal Surfactant System

The adult human lung is composed of approximately 300 million alveoli. The tendency of alveoli to collapse is greatest at end-expiration when its size is smallest. However, normal alveoli do not collapse primarily because of two factors: (1) the structural interdependence of adjacent alveoli that tends to tether collapsing or collapsed alveoli and (2) the surface-tension-reducing substance that lines the alveoli and bronchioles—surfactant.[1]

### Function

Pulmonary surfactant is a complex surface-active substance produced in the type-II pneumocytes that comprise the alveolar surface. This substance forms a monolayer—a film with the thickness of only one molecule—on the alveolar surface

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and the narrow, conducting airways.[2] Surfactant acts to vary the surface tension at the air-liquid interface of lung units, increasing the surface tension during lung inflation and decreasing it during deflation. The Law of Laplace demonstrates this principle.

$$P = 2\ \frac{T}{r}\ ;\ \text{therefore,}\ T = P\ \frac{r}{2}\ ;$$

where P is the pressure inside the alveolus, $T$ is the alveolar wall surface tension, and $r$ is the alveolar radius.

If surface tension were constant and did not vary during the respiratory cycle, small alveoli would empty into large alveoli because the pressure is greater in the small alveoli than in the large ones, and gas molecules seek pressure equilibrium.[1,3,4]

Surface tension is responsible for the hysteresis seen on the pressure-volume curve of lung inflation.[1,5] Figure 1 shows that when the lung is inflated with saline, the hysteresis, or the area circumscribed by the inspiratory and expiratory limbs of the pressure-volume curve, is minimal. This occurs because a liquid-liquid interface exists at the alveolar level, minimizing surface tension. In this setting, the hysteresis of the pressure-volume curve is primarily due to lung-tissue recoil. When the lung is inflated with air, a substantial amount of pressure is required to overcome surface tension at the air-liquid interface before lung units open and volume is delivered. This pressure-volume curve represents the elastic components of both the lung-tissue and the surface-tension forces. The slope of the pressure-volume curve or the change in volume with each unit pressure change defines compliance. Pulmonary surfactant decreases alveolar surface tension and improves compliance and functional residual capacity (FRC), thereby reducing the work of breathing and improving gas exchange.

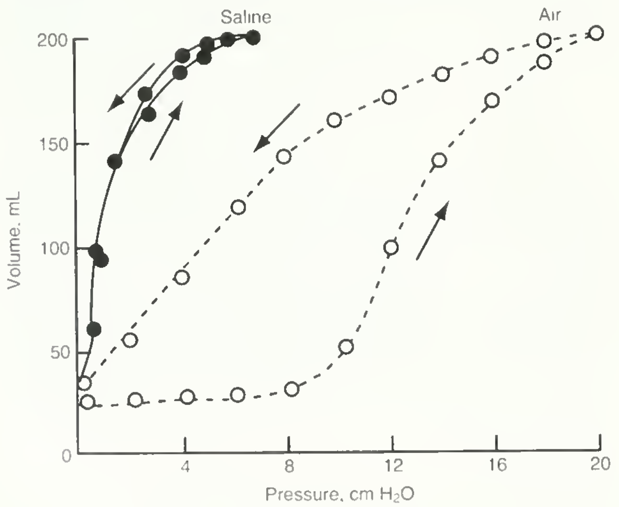

Fig 1. Volume-pressure curves of excised cat lungs inflated with either saline or air. The curve represented with the solid line shows the relative absence of hysteresis during saline inflation, compared to air inflation (dashed line). (From Reference 5, with permission)

## Composition

Pulmonary surfactant is composed primarily of phospholipids, neutral lipids, and surfactant-specific proteins (also called apoproteins) (Table 1). The composition of pulmonary surfactant is similar among many mammalian species.[4] Phospholipids comprise 80-90% of the surfactant by weight, neutral lipids about 2-10%, and proteins 5-10%.[6-8]

Table 1. Composition of Human Pulmonary Surfactant

| Component | % Total | % PL | % PC |
|---|---|---|---|
| Phospholipids (PL) | 80-90 | | |
| Phosphatidylcholine (PC) | | 80 | |
| Dipalmitoylphosphatidylcholine | | | 50 |
| Unsaturated PC | | | 20 |
| Phosphatidylglycerol | | 10 | |
| Phosphatidylethanolamine | | 3-5 | |
| Phosphatidylserine | | 2-3 | |
| Phosphatidylinositol | | 3-4 | |
| Sphingomyelin | | 1-3 | |
| Proteins (SP-A, SP-B, SP-C, SP-D) | 5-10 | | |
| Neutral lipids<br>(Cholesterol, triglyceride, free fatty acids) | 2-10 | | |

Phosphatidylcholine (PC) comprises approximately 80% of the phospholipid, and the disaturated PC, dipalmitoylphosphatidylcholine (DPPC), is the largest PC component. DPPC is the principle surface-active phospholipid. Phosphatidylglycerol (PG) is the second most abundant and important phospholipid, and is approximately 10% of the phospholipid component. The neutral lipids include cholesterol, triglyceride, and free fatty acids.

Three proteins specific to pulmonary surfactant appear to be important to the effectiveness of surfactant.[9-11] The first surfactant protein, SP-A, is a large (molecular weight 26-36 kD, depending on degree of reduction), hydrophilic, collagenous protein[12] and comprises 30-40% of the total surfactant-associated protein.[9,13] It is involved with surfactant secretion and recycling, and may also enhance adsorption, a characteristic of surfactant.[14] SP-A also contributes to tubular myelin formation in the alveolus and counteracts the inhibition of surfactant by albumin and fibrin.[15] SP-B and SP-C are small (molecular weight 8 and 5 kD in their reduced state), noncollagenous, highly hydrophobic proteins. They dissolve in organic solvents and account for 1-2% of the surfactant weight.[11] Both proteins facilitate the adsorption and spreading of phospholipids to form the surface-active monolayer.[11] Although apparently not essential for surfactant function, SP-A, in the presence of calcium, acts synergistically with SP-B to increase lipid adsorption and to decrease surface tension. Another large (45 kD), collagenous surfactant protein, SP-D, has recently been described.[16] Its function has yet to be delineated. However, it is possible that SP-D, along with SP-A, may play a role in the host-defense mechanisms of the lung.

### Metabolism

Surfactant is synthesized in the endoplasmic reticulum of type-II cells and transferred by the Golgi apparatus to prelamellar bodies where it matures and is packaged as lamellar bodies (Fig. 2).[17-19] The tightly packed lamellar bodies are secreted into the alveolus where they unravel to form tubular myelin (TM) structures. Acting as a reservoir for surfactant molecules, TM is a loose lattice of phospholipids and surfactant proteins that easily adsorb and spread to form the surface-active monolayer at the air-liquid interface. Respiratory movements expand or stretch the monolayer during inspiration and compress it during expiration. During inspiration to total lung capacity (TLC), the TM adsorbs to patches of the stretched and now relatively bare alveolar surface that are then covered by the rapid spreading of new surfactant.[20] When compressed during expiration to FRC, the unsaturated phospholipids and proteins are 'squeezed out' of the film, leaving a relatively pure concentration of DPPC that is capable of lowering surface tension.[11,20] Thus, the surface film is dynamic—it is continually recycled and is likely modulated to a large degree by the respiratory cycle.[18] In addition to the normal respiratory cycle, hyperventilation, $\beta$-adrenergic agents, and cholinergic agents can stimulate pulmonary surfactant secretion.[6,10,21]

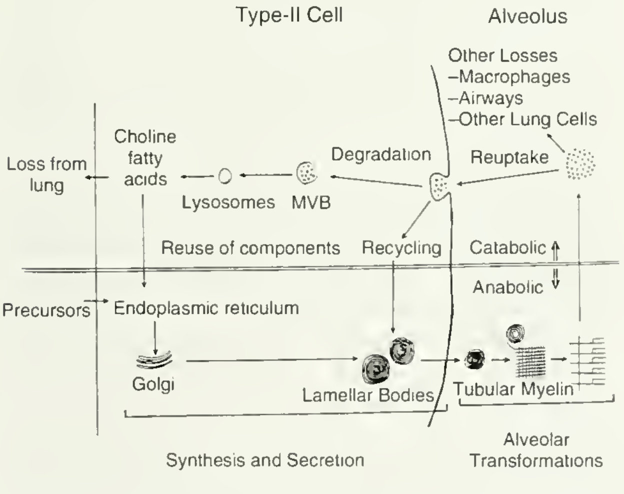

Fig 2. Cellular synthesis, excretion, and reuptake of pulmonary surfactant. MVB = multivesicular bodies (Modified from Reference 12, with permission)

Under normal conditions, surfactant is secreted at a fairly rapid rate, estimated to be 11-40% of the alveolar lipid pool/hour.[19] To maintain a consistent pool size, surfactant is removed from the alveolar airspace via the processes of recycling and degradation. Of the surfactant secreted, 90-95% is recycled. Most of the surfactant components squeezed out of the monolayer during compression enter the hypophase, the water layer below the surfactant film, and re-enter the type-II cell where they are either incorporated into the lamellar bodies and resecreted (recycled) or catabolized. Surfactant that is not recycled is catabolized by the type-II cells (70%) or macrophages (30%). Normally, about 50% of the PC is degraded within 2 hours.[10] Very little of the surfactant is lost via the lung lymphatics and no more than 2-5% is lost via the airways.[18]

### Pulmonary Surfactant & Respiratory Failure

In 1959, Avery and Mead[22] observed that the surface-active substance present in the lungs of adults, children, and newborns larger than 1,100-1,200 g was deficient in the lung extracts of 9 premature infants who had died of hyaline membrane disease. This observation was an important stimulus for the study of pulmonary surfactant.[7] Subsequent research demonstrated that the most common cause of RDS is premature birth—ie, birth before the pulmonary surfactant system is fully developed. Surfactant begins forming at about 4-months gestation, but is not fully functional until at least the seventh month.[1]

Although described in pieces and known by a variety of names throughout several decades, Ashbaugh and associates[23] in 1967 provided the first description of what came to be called the acute respiratory distress syndrome (ARDS) of the adult.[24] They reported that the minimum surface tension of minced lung surfactant from two deceased patients with ARDS was >20 dyn/cm. Normal surface tension is <10 dyn/cm. These investigators suggested that surfactant dysfunction was responsible for the pattern of pulmonary pathophysiology common to the multi-etiologic lung injuries seen in patients with ARDS.

The pathophysiology common to both RDS and ARDS includes atelectasis, reduced compliance and FRC, and intrapulmonary shunting with hypoxemia—all associated with abnormal pulmonary surfactant. Surfactant deficiency has been identified as the primary cause of RDS, but it is much harder to establish such a relationship in ARDS because of the multitude of inflammatory mediators involved and because of its varied etiology. Although the etiologies of ARDS are many, the disease progresses along two basic pathways (Fig. 3)—injury to the alveolar epithelium via the airways (eg, smoke, infection, aspiration, hyperoxia) or injury of the alveolar endothelium via the blood (eg, sepsis, drugs, shock, burns). Regardless of the pathway, the result is an inflammatory response with cellular and humoral components and, ultimately, cell injury and surfactant impairment. Several recent reviews offer a detailed discussion of ARDS.[25-27] Four possible mechanisms responsible for abnormal surfactant function in ARDS have been described: (1) pool size, (2) composition, (3) metabolism, and (4) functionality (inactivation).[12,28,29]

From the results of lung lavage procedures, it has been estimated that adult animals (rabbits, sheep, monkeys) have an alveolar surfactant pool size of 10-15 mg lipid/kg body weight;[18] the only calculated measurement for humans, 3 mg lipid/kg, is thought to be a low estimate.[12] Accurate measure-

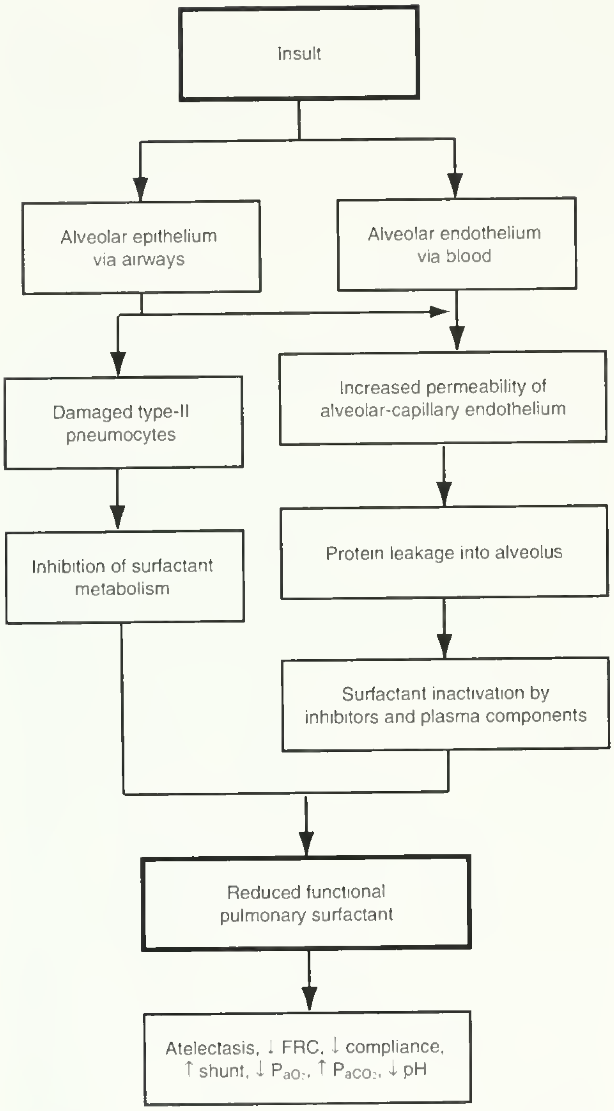
Insult
Alveolar epithelium via airways
Alveolar endothelium via blood
Damaged type-II pneumocytes
Increased permeability of alveolar-capillary endothelium
Inhibition of surfactant metabolism
Protein leakage into alveolus
Surfactant inactivation by inhibitors and plasma components
Reduced functional pulmonary surfactant
Atelectasis, ↓ FRC, ↓ compliance, ↑ shunt, ↓ $P_{aO_2}$, ↑ $P_{aCO_2}$, ↓ pH

Fig. 3. Possible pathogenesis of ARDS as shown from the perspectives of both airborne and blood-borne injury.

ments in patients are hard to obtain because the sample consists of a relatively small amount of bronchoalveolar lavage (BAL) fluid recovered from an isolated lung region using a technique that is not standardized.[12] As a result, pool size has been expressed as: (1) a percentage of various surfactant components of the total phospholipid recovered, (2) the phosphatidylcholine (lecithin) to sphingomyelin ratio (L/S), or (3) the ratio of large to small alveolar surfactant aggregates.

Three human studies present conflicting data regarding pool size. Hallman and colleagues[30] observed a small, nonsignificant difference in the phospholipid concentration of BAL specimens from 36 patients with ARDS/respiratory failure and 12 patients with healthy lungs. Pison and colleagues[31] did not observe a significant change in phospholipid concentrations in their BAL samples from 17 patients with multiple trauma and 10 patients with healthy lungs. Their findings contrast with those of Gregory and colleagues[32] who documented a decrease in BAL phospholipids in their population of 20 patients at risk to develop ARDS and 66 patients with ARDS, compared to 29 patients without lung disease. Although these studies do not conclusively demonstrate a change in pool size with lung injury, it has been speculated[12,28] that pool size may be determined by the type and severity of lung insult—that acute, severe injury of type-II cells may decrease the surfactant pool and that chronic injuries, resulting in a hyperplastic type-II-cell response, may increase the size of the phospholipid pool.[12,29]

Although the size of the phospholipid pool has not definitively been shown to change, studies have documented significant changes in the composition of pulmonary surfactant following lung injury. Table 2 shows the relative changes in phospholipid composition in the three studies cited in the previous paragraph.[30-32] The relative amounts of phosphatidylcholine (PC) and phosphatidylglycerol (PG) are decreased and those of phosphatidylinositol (PI), phosphatidylethanolamine (PE), and sphingomyelin are increased following lung injury. Similar findings have been seen in adult rabbits due to lung

Table 2. Change in Human Phospholipid Composition Related to the Acute Respiratory Distress Syndrome (ARDS) Expressed as a Percentage of Total Phospholipid.

| Lipid Component | Hallman[30] |  | Pison[31] |  |  | Gregory[32] |  |  |
|---|---|---|---|---|---|---|---|---|
|  | Normal (n = 12) | ARDS (n = 36) | Normal (n = 10) | High ARDS Score (n =10) | Low ARDS Score (n = 7) | Normal (n = 29) | At-risk (n = 20) | ARDS (n = 66) |
| PC | 73.0 | 59.6 | 62.8 | 56.3 | 48.1 | 76.3 | 73.3 | 62.6 |
| PG | 12.4 | 0.3 | 10.0 | 1.6 | 1.9 | 11.6 | 7.3 | 6.5 |
| PI | 2.7 | 3.1 | 8.3 | 13.5 | 13.9 | 3.9 | 4.7 | 6.9 |
| PE | 2.6 | 4.3 | 4.8 | 13.6 | 18.7 | 3.3 | 4.9 | 5.9 |
| PS | 3.3 | 13.0 | 4.5 | ND | ND | 1.8 | 3.8 | 2.8 |
| Sph | 3.7 | 17.5 | 7.4 | 12.3 | 14.2 | 1.5 | 1.6 | 5.5 |

PC = phosphatidylcholine; PG = phosphatidylglycerol; PI = phosphatidylinositol; PE = phosphatidylethanolamine; PS = phosphatidylserine; Sph = sphingomyelin. ND = no data.

injury induced by oleic acid,[33] N-nitroso-N-methylurethane (NNNMU),[34] and vagotomy.[35]

In addition to changes in the phospholipid composition, the level of surfactant apoproteins also changes during ARDS. Gregory and colleagues[32] demonstrated that ARDS patients have reduced SP-A and SP-B, and that patents at risk for ARDS have a reduced SP-A compared to subjects with healthy lungs (Table 3). Surface tension increases as the surfactant protein level decreases. Pison and colleagues[36] demonstrated reduced SP-A (SP-B was not measured) in the BAL fluid of 19 patients with multiple trauma. SP-A concentration decreased early following trauma and decreased in proportion to the severity of lung injury—in severe injury SP-A dropped to approximately 1.0 μg/mL and rose only to about 1.4 μg/mL by Day 18 (control, 2.74 μg/mL) whereas moderate lung injury initially dropped to approximately 1.6 μg/mL, rose to 4.1 μg/mL during the intermediate stage (3-6 days), and then decreased to 2.45 μg/mL during the late phase (7-18 days).

Table 3. Mean (SD) Concentration and Surface Tension of Surfactant-Associated Proteins in Bronchoalveolar Lavage of Patients with Acute Respiratory Distress Syndrome (ARDS)[32]

| | Surfactant-Associated Proteins (μg/mL) | | Surface Tension (dyn/cm) | |
|---|---|---|---|---|
| | SP-A | SP-B | Minimum | Maximum |
| Normal | 123.6 (20.7) | 1.28 (0.33) | 7.44 (1.61) | 35.76 (1.97) |
| At-Risk | 49.3 (21.7) | 0.89 (0.54) | 15.10 (2.53) | 44.56 (2.74) |
| ARDS | 8.5 (6.2) | 0.57 (0.24) | 29.04 (2.05) | 53.03 (1.77) |

The changes in the size and composition of the surfactant pool may be related to altered metabolic function of the alveolar type-II cells due to acute lung injury.[12,34] In addition to the change of metabolism of the type-II cells, changes in the intra-alveolar metabolism of surfactant—the breakdown of surfactant within the alveolus—are also apparent. Surfactant exists within the alveolus in various aggregate forms that differ in size, density, composition, and function. Large or heavy aggregates are rich with tubular myelin and have good surface-tension-lowering capabilities. The large aggregates are metabolically converted within the alveolar space to smaller, lighter aggregate forms that are less surface active.[34,37] Normally the ratio of small-aggregate (SA) to large-aggregate (LA) forms is approximately 1:1, but with lung injury the small aggregate increases and the large aggregate declines. Lewis and colleagues[34] demonstrated with NNNMU-induced lung injury in rabbits that SA:LA increased by 5-fold by the fourth day after the injury. This conversion was inhibited by the addition of >3% SP-A to the large-aggregate sample. The composition of the aggregates also changed with lung injury—the small aggregate had reduced PG and increased PI and sphingomyelin. The large-aggregate form had much better surface-tension-lowering capabilities compared to the small-aggregate form. This observation was confirmed by Veldhuizen and colleagues[38] and by Higuchi et al.[37] It has been speculated that "...the forms of surfactant within the alveolus may be a far more important variable in lung injury than the total size of the surfactant pool."[12]

The fourth and probably one of the most important factors leading to abnormal surfactant function in lung injury is surfactant inactivation (Fig. 3). One of the earliest pathogenic events of ARDS is damage to the alveolocapillary membrane and subsequent leakage of plasma proteins, cell-membrane lipids, and hemoglobin into the alveolar space.[39] The protein molecules interfere with the formation of the surface-active monolayer by competing with the surfactant molecules for positions on the alveolar surface. Kobayashi and colleagues[40] demonstrated that the surface-tension-lowering capability of surfactant and various levels of edema fluid obtained from rabbits with hyperoxic lung damage were inversely proportional to the ratio of protein to lipid (P/L); therefore, as edema fluid and P/L increase, the minimum surface tension increases.

Degraded fibrin products and fibrinogen have more potential to inhibit surfactant than does albumin. Studies suggest that phospholipids, and possibly SP-B and SP-C, are incorporated into or bound to fibrin strands and hyaline membranes, thereby reducing functional surface-tension-reducing activity.[28] The specific serum protein, the concentration of the protein relative to the concentration of endogenous surfactant, and the presence of other potential inhibitors are determinants of surfactant inactivation.[12,35] Recent evidence suggests that SP-A protects surfactant against the inhibitory effects of plasma in vivo.[15] The effects of inactivation can be overcome by increasing the size of the surfactant pool with exogenous surfactant.[15,40,41]

Pulmonary surfactant may also have a role in the lung's host-defense and immune responses and, therefore, may play an important role in ARDS.[12] Although surfactant isolated from normal lungs increases the movement and phagocytic activity of alveolar macrophages, the relationship between macrophage activity and ARDS is unclear. Surfactant also acts as a lubricant to protect the airways and promote mucociliary transport.[42] At end-expiration, lung volume is reduced and the surface film moves from the alveoli to the bronchioles where damaged cells and particulate matter can be removed by the mucociliary escalator.

## Exogenous Surfactant Therapy

### Preparations

There are two broad types of exogenous surfactants—synthetic and natural. Synthetic surfactants made in the laboratory contain DPPC and various adsorbing and spreading agents. Natural surfactants come from lungs of humans or mammalian animals. Human surfactant is taken from amniotic fluid. Animal surfactant is extracted from either alveolar lavage fluid or minced lung extract, usually from cows or pigs. A purported advantage of the natural surfactants is that they contain apoproteins—both human and animal extracts contain SP-B and SP-C, whereas the human surfactant also contains SP-A. Table 4 reviews the various exogenous surfactants that have been used, albeit primarily in neonates.

Two synthetic surfactants have been evaluated in large clinical trials (ALEC and Exosurf) and a third is under development ($KL_4$). Artificial lung expanding compound (ALEC) is available as either a powder or liquid suspension and has been studied primarily in England.[43-46] It is a mixture of 70% DPPC and 30% PG. Exosurf has been extensively studied[47-59] and, in the United States, has been approved for use in neonates. It consists of DPPC, hexadecanol, and tyloxapol. In both of these preparations, DPPC is the primary surface-active agent and the other ingredients facilitate surface adsorption and spreading. $KL_4$ is a synthetic peptide having SP-B-like properties. Combinations of this peptide and DPPC are being evaluated.[60]

The natural surfactant, Surfactant TA, was introduced, tested,[52,61-64] and approved for neonatal use as Survanta in the United States (Surfacten in Japan). It is prepared by extracting lipids, SP-B, and SP-C from minced bovine lungs using organic solvents. Additional DPPC, palmitic acid, and tripalmitin are added to give the extract a composition similar to that of human surfactant (without the SP-A).[42,65] Curosurf is an organic solvent extract of minced pig lung with the neutral lipids removed by gel chromatography. The extra purification process improves the surface properties of this type of surfactant.[65] Organic solvents can also be used to remove the lipid, SP-B, and SP-C components from alveolar-lavage fluid. This type of process is used with calf lungs to produce Infasurf. This preparation is also known as calf-lung surfactant extract or CLSE. A similar process is used with adult cow lungs to produce Alveofact.[42,65] Currently only Exosurf and Survanta have been approved by the Food and Drug Administration to be used in the United States for neonates at risk for (prophylactic therapy) or having (rescue therapy) RDS.

## Response to Therapy

The strength of the evidence for exogenous surfactant replacement therapy depends on

- the model—whether the study was conducted in a laboratory model (in vitro) or in humans or mammals (in vivo) and which species (eg, rat, rabbit, sheep, or primate) was used. The results of animal studies may not apply directly to treatment of human disease because of the biologic variation among species and because the timing of injury and intervention is usually very different between the laboratory and the clinical setting.
- the age of the subjects (whether they are premature newborns or adults);
- the lung injury method—alveolar lavage simulates surfactant deficiency seen in RDS and has certain similarities to ARDS.[66] Other ARDS models have been created using NNNMU,[34,67,68] oleic acid,[33,69,70] bile,[71] hydrochloric acid,[72] anti-lung serum,[39,66] 100% oxygen,[66,73-75] bilateral cervical vagotomy,[35] and viral infection.[66,76] The lung and other organs respond differently to each insult.

Table 4. Exogenous Surfactant Preparations: Source and Composition

| Preparations | Source | Composition |
|---|---|---|
| **Synthetic surfactants** | | |
| ALEC* (Pulmactant, Brittania, Red Hill, Surry, United Kingdom) | Synthetic | DPPC*, unsaturated phosphatidylglycerol |
| Colfosceril palmitate (Exosurf, GlaxoWellcome, Research Triangle Park NC) | Synthetic | DPPC, hexadecanol, tyloxapol |
| $KL_4$ | Synthetic | DPPC, $KL_4$ |
| **Natural human surfactant** | | |
| Human | Amniotic fluid | Surfactant lipids, SP-A, SP-B, SP-C |
| **Natural animal surfactants** | | |
| Alveofact (Thomae, Bilberach, Germany) | Lipid extract of cow lung lavage | Surfactant lipids, SP-B, SP-C |
| CLSE* (Infasurf, Forest Laboratories, St Louis MO) | Lipid extract of calf lung lavage | Surfactant lipids, SP-B, SP-C |
| Curosurf (Chiesi Farmaceutici, Parma, Italy) | Organic solvent of pig lung purified by chromatography | Lung phospholipids, SP-B, SP-C |
| Surfactant-TA (Surfacten, Tokyo Tanabe, Tokyo Japan and beractant [Survanta] Ross Laboratories, Columbus OH) | Lipid extract of cow lung and synthetic lipids | Lung lipids, DPPC, tripalmitin, palmitic acid |

Abbreviations: ALEC, artificial lung expanding compound; DPPC, dipalmitoylphosphatidylcholine; CLSE, calf-lung-surfactant extract.

- the surfactant preparation itself—in addition to the preparations listed in Table 4, many researchers make their own extractions.
- the dose administered and the delivery method—was the surfactant instilled as a bolus via the endotracheal tube or a bronchoscope, or was it aerosolized? Was the subject mechanically ventilated? What $V_T$, positive end-expiratory pressure (PEEP), inspiratory pressure, and I:E were used? and
- the measures of efficacy—what variables were chosen to indicate a favorable outcome—ie, gas exchange, respiratory mechanics, changes in alveolar lavage fluid (composition and surface activity), mortality?

Taken together, these factors make it difficult to analyze the volumes of data that have accumulated.

## Effects

In addition to the previously described benefit of decreasing inactivation of endogenous surfactant by serum proteins, several other effects of exogenous surfactant have been described. Matalon and colleagues [77] demonstrated that exogenous surfactant can mitigate the progression of hyperoxic lung injury in adult rabbits exposed to 100% oxygen for 64 hours. They instilled 125 mg of CLSE at 0 and 12 hours following exposure to 100% oxygen and found increased lung phospholipids (34 vs 4.5 $\mu$mol/kg), increased TLC (42 vs 27 mL/kg), decreased alveolar protein (36 vs 56 mg/kg) and decreased atelectasis as evidenced by $P_{aO_2}$ increased to 460 torr from 197 torr. Similar effects have been observed using instilled Exosurf with adult rats[78] and aerosolized Exosurf with adult baboons.[73,74]

Using the same lung model and surfactant as Matalon and colleagues, Novotny et al[75] demonstrated that hyperoxic lung injury can reduce exogenous surfactant clearance in vivo. This is probably due to injury of the alveolar type-II cells and their ability to recycle surfactant components in the monolayer. If the surfactant present in the monolayer is the large-aggregate type and is otherwise functioning well, the reduced clearance may prolong the effectiveness of therapy. These observations may be important in determining dosing regimens for surfactant.[75]

Ikegami and colleagues[79] speculated that exogenous surfactant might be activated by some components of endogenous surfactant in preterm lambs. Following surfactant administration and ventilation for 5 hours, alveolar lavage was performed. Preterm rabbits were given either the original treatment surfactant, the large- or small-aggregate surfactant recovered from the lamb lavage fluid, or nothing. It was found that the large-aggregate surfactant recovered from the treated lambs performed better than did the original treatment surfactant, indicating that the exogenous surfactant was activated and its functionality enhanced by having been in the preterm lambs' lung.

Exogenous surfactant also has anti-inflammatory effects. Synthetic surfactant has been shown to inhibit tumor necrosis factor (TNF) production,[80,81] suppress interleukin-1 and interleukin-2,[81,82] and inhibit endotoxin-stimulated cytokine secretion of human alveolar macrophages.[83]

## Comparisons among Preparations

Cummings and colleagues[84] compared 4 exogenous surfactant preparations in vivo. Surfactant was instilled into surfactant-deficient preterm lambs. Exosurf was instilled as two 2.5 mL aliquots over 1-3 minutes, whereas Infasurf, Survanta, and natural sheep surfactant were given as intratracheal boluses into fluid-filled lungs before ventilation was begun. A second surfactant dose was given after 12 hours if the $P_{aO_2}$ was <100 torr while breathing 100% oxygen and receiving maximal ventilatory support. Table 5 shows that although Survanta, Infasurf, and the sheep extract significantly increased survival,

Table 5. Comparison of Four Exogenous Surfactants[84]

| Variable | Control | Exosurf | Survanta | Infasurf | Sheep Extract |
|---|---|---|---|---|---|
| Survival at 12 h (%) | 0 | 0 | 50 | 85 | 20 |
| Survival at 24 h (%) | 0 | 0 | 33 | 67 | 20 |
| Survivors meeting retreatment criteria at 12 h | NA* | NA* | 2/2 | 1/5 | 1/1 |
| $P_{aO_2}$ immediately after instillation (0 h) | 44 | 72 | 223 | 290 | 292 |
| $P_{aO_2}$ at 12 h | NA | NA | 100$^{\dagger}$ | 250$^{\dagger}$ | 50$^{\dagger}$ |
| VEI$^{\ddagger}$ (0 h) | 0.022 | 0.022 | 0.064 | 0.140 | 0.163 |
| VEI at 12 h | 0.015$^{\S}$ | 0.030$^{\|}$ | 0.040 | 0.140 | 0.043 |
| Minimum surface tension | 30 | 22 | 17 | 11 | 12 |

*All animals expired by 12 hours; $^{\dagger}$ values are approximations taken from an x-y plot; $^{\S}$ at 7 hours; $^{\|}$at 8 hours; NA, not applicable

$^{\ddagger}$ VEI = ventilatory efficiency index = $\dfrac{\dot{V}_{CO_2}}{(\text{PIP} - \text{PEEP})(\text{rate})\left(\dfrac{P_{aCO_2}}{760 \text{ torr}}\right)}$,

where PIP = peak inspiratory pressure, PEEP = positive end-expiratory pressure, 760 torr = barometric pressure at sea level, $\dot{V}_{CO_2}$ = $CO_2$ elimination assumed to be cons
at 5 mL · kg$^{-1}$ min$^{-1}$

ventilatory efficiency index, and initial response to oxygen, only Infasurf maintained these improvements. Infasurf also had the best static deflation pressure-volume curve (Fig. 4). Exosurf performed no better than controls in any regard.

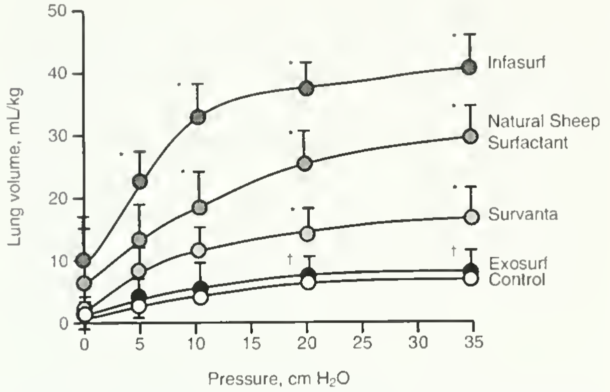

Fig. 4. Effect of four exogenous surfactants on the deflation limb of the pressure-volume curve. * indicates $p < 0.02$ compared to control group; † indicates $p < 0.02$ compared with natural sheep surfactant group. (From Reference 84, with permission.)

Ikegami and colleagues[79] observed similar results with preterm lambs. They compared Survanta, Exosurf, and two noncommercial synthetic mixtures. Both noncommercial mixtures contained a mixture of 69% DPPC, 22% PG, and 9% palmitic acid. However, one mixture was prepared by heat annealing (Mixture 1) and the other mixed using glass beads (Mixture 2). Survanta was found to decrease ventilatory pressure and improve compliance and the ventilatory efficiency index, followed by Mixture 1, Mixture 2, and Exosurf. Five hours after surfactant administration, alveolar wash demonstrated significantly more of the Survanta remaining in the large-aggregate form than the Exosurf, and this large-aggregate fraction contained more SP-A than did the other preparations.

Hall and colleagues[85] did an in-vitro comparison of CLSE, Survanta, and Exosurf. Because the first two preparations contained apoproteins, SP-B and SP-C were added to Exosurf for this evaluation. Table 6 shows the four surfactant preparations with their ability to adsorb, to lower surface tension during compression with and without the presence of albumin, and to restore pressure-volume lung mechanics. CLSE provided the best surfactant-like characteristics, followed closely by Survanta. Exosurf performed poorly until the apoproteins were added, after which its performance was similar to CLSE and Survanta.

Table 6. Effect of Proteins in Exogenous Surfactant[85]

| | CLSE | Survanta | Exosurf | Exosurf + SP-B + SP-C |
|---|---|---|---|---|
| Adsorption (final surface tension [ST]) (mN/m) | 22 | 28 | 38 | 32† |
| Minimum ST (mN/m) | <1 | <2 | 29 | 1 |
| Minimum ST+ 20 mg/mL albumin* (mN/m) | <1 | <2 | 30 | 1† |
| Ability to restore lung mechanics (%) | 100* | 50 | <10 | 70† |

* 2.5 mg/mL surfactant used with Survanta and calf-lung-surfactant extract, 10 mg/mL with Exosurf. † Values are approximations taken from x-y plots.

Survanta and Exosurf were compared in a prospective, randomized clinical study of over 600 infants with RDS.[52] Although there was a small difference in the initial $F_{IO_2}$ and mean airway-pressure response favoring Survanta, no differences in mortality or incidence of bronchopulmonary dysplasia (BPD) was found between the two surfactant preparations at 28 days.

## Exogenous Surfactant Use in Humans

### Neonates

The first administration of surfactant to neonates was reported in 1980 by Fujiwara and colleagues,[86] and since then thousands of infants have been treated with surfactant.[59,61,65,87,88] Surfactant replacement therapy has become such a standard of care that the American Association for Respiratory Care has developed a clinical practice guideline [89] to assist practitioners in its administration.

Surfactant therapy in preterm infants has been one of the most thoroughly studied new therapies in neonatal care.[65] More than 40 randomized, controlled trials have been reported since 1985; several of the larger studies are listed in Table 7. It is clear that surfactant therapy can reduce mortality, air leaks, the need for mechanical ventilation and oxygen therapy, and the severity of RDS; it can improve pulmonary mechanics and gas exchange. The incidence of BPD has not changed dramatically, but this may be related to the 'survival effect'—the fact that more infants treated with surfactant survive, and these survivors are at high risk for BPD.

The most serious complication reported in neonates treated with surfactant is pulmonary hemorrhage. A meta-analysis[87] of 29 studies published between 1980-1992 demonstrated a pulmonary hemorrhage rate of approximately 2.7% for all infants with RDS (> 5,000 infants); this increased by 47% with surfactant—from 2.1% for the controls to 3.7% for the surfactant group (Table 8). Although the side effects appear to be minimal and their frequency low, concern has been raised about administering therapy to patients who do not need it.[87]

The primary strategies for administering exogenous surfactant to infants is to give it either immediately at birth (prophylaxis) to patients at risk for RDS (< 32-weeks gestation

Table 7. Human Infant Studies of Exogenous Surfactant Therapy

| Surfactant | Patients (n) | Study Type | Treatment Criteria | Outcome Variables | First Author, Year |
|---|---|---|---|---|---|
| ALEC | 149 control<br>159 study | Prospective, randomized, placebo-controlled study | 25-29 weeks gestation | Decreased mortality (27 vs 14%), time ventilated, brain hemorrhage | Ten Centre, 1987[43] |
| Alveofact | 35 control<br>34 surfactant | Prospective, randomized, placebo-controlled study | 23-30 weeks gestation, instill 50 mg/kg ≤ 1 h after birth, up to 3 doses | Increased survival without BPD* (76 vs 40%) | Gortner, 1992[90] |
| Bovine, Porcine | 263 control<br>277 study | Meta-analysis of 7 studies | RDS*, single dose before first breath or within 15 min | Decreased mortality (30 vs 20%) and pneumothoraces (37 vs 16%) | Heenes, 1991[88] |
| CLSE | 31 control<br>34 surfactant | Prospective, randomized, placebo-controlled study | 25-29 weeks gestation, single dose, prophylactic | Decreased severity of RDS within first 24 h but not sustained; decreased pneumothoraces; multiple doses may improve effect | Kendig, 1988[91] |
| Curosurf | 1,069 low dose<br>1,099 high dose | Prospective, randomized study | RDS, low dose = 100 mg/kg initial, at 12 h and 24 h (up to 300 mg/kg); high dose = 200 mg/kg initial, 100 mg/kg × 4 (maximum 600 mg/kg) | No difference | Halliday, 1993[92] |
| Exosurf | 213 control<br>206 study | Prospective, randomized, placebo-controlled study | 700-1,350 g RDS; 2 rescue doses:<br>1st—2-24 h<br>2nd—12 h later | Decreased $P_{(A-a)O_2}$, $F_{IO_2}$, and ventilatory needs; fewer deaths from RDS (21 vs 7%), mortality (50 vs 23%) | Long, 1991[53] |
| Exosurf | 222 control<br>224 study | Prospective, randomized, placebo-controlled study | 700-1,100 g RDS, 1 rescue dose, as soon as possible after birth | Decreased oxygen needs; fewer air leaks and RDS deaths; 28 day mortality (20 vs 13%) | Corbet, 1991[51] |
| Exosurf | 1,344 early,<br>1,346 late,<br>3,381 × 2 doses,<br>3,376 × 4 doses | Prospective, randomized, controlled, open label study | Early: < 2 hours after birth, high risk for RDS, intubated;<br>late: > 2 hours old, clinical diagnosis of RDS | Early: decreased air leaks;<br>25% treated unnecessarily;<br>no advantage to >2 doses | OSIRIS 1992[59] |
| Exosurf vs Survanta | 309 Exosurf<br>308 Survanta | Prospective, randomized study | 501-1,500 g RDS, up to 4 doses | No difference in mortality or BPD | Horbar, 1993[52] |
| Survanta | 28 control<br>28 study | Prospective, randomized, placebo-controlled study | >34 weeks gestation, on ECMO, 4 doses | Decreased ECMO* time and complications (46 vs 18%); improved pulmonary mechanics | Lotze, 1993[62] |
| Survanta | 156 control<br>154 study | Prospective, randomized, placebo-controlled study | 23-26 weeks gestation | Decreased mortality (45 vs 27%) | Ferrara, 1994[64] |
| Survanta | 2,670 early<br>5,498 late | Prospective, open label, TIND* study | early: 1 dose at birth if 600-1,250 g<br>late: 1 dose if 600-1,750 g with RDS;<br>all could receive up to 4 doses within a 48 hour period | Decrease in intracranial hemorrhage, air leaks, BPD, and sepsis compared to treated neonates in controlled trials; no safety concerns | Zola, 1993[61] |

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* RDS, respiratory distress syndrome; BPD, bronchopulmonary dysplasia; ECMO, extracorporeal membrane oxygenation; TIND, treatment investigational new drug

Table 8. Incidence of Pulmonary Hemorrhage in Neonates[87]

| | % All Patients (n/N) | % Control (n/N) | % Surfactant (n/N) |
|---|---|---|---|
| 4 Natural Surfactant Studies | 5.6(78/1,388) | 5.4 (37/690) | 5.9(41/698) |
| 7 Synthetic Surfactants Studies | 1.8(51/2,880) | 1.0 (15/1,448) | 2.5(36/1,432) |
| Surfactant Type Not Stated (15 Studies) | 1.3(12/932) | 0.3 (1/391) | 2 (11/541) |
| All Studies | 2.7(141/5,200) | 2.1 (53/2,529) | 3.7(88/2,671) |

or < 1,300-g birthweight) or as a therapeutic dose (rescue) to patients with clinical evidence of RDS.[89] Whereas some studies have found that giving the surfactant early is beneficial,[59] others have found no difference.[88] It has been stated that as many as 40% of infants < 30 weeks gestation receive prophylactic surfactant unnecessarily.[93]

Several large studies have evaluated the long-term effects of surfactant therapy in neonates (Table 9). Not only does exogenous surfactant therapy reduce mortality and morbidity, it does not appear to interfere with normal growth and neurodevelopment.[47,49,50,54,55,94,95] Longer term follow-up evaluations are ongoing.

## Adults

Few studies of exogenous surfactant therapy have been reported in ARDS patients (Table 10). In 1989, Richman and

Table 9. Exogenous Surfactant Replacement Studies in Human Infants: Results of Long-Term Follow Up

| Surfactant | Patients (n) | Study Type | Treatment Criteria | Outcome Variables | First Author, Year |
|---|---|---|---|---|---|
| Exosurf | 13 control<br>34 study | Reporting 6- and 12-mo follow up of prospective, randomized, placebo-controlled study | >1,000 g, RDS*, 2 rescue doses: 2-24 h and 12 h later | Decreased days on ventilator and $O_2$; fewer patients discharged with bronchodilators; increased expiratory flow by age 1 year | Abbasi, 1993[47] |
| Exosurf | All 826 received initial surfactant dose; 410 received 2 or 3 placebo doses; 416 received 2 or 3 doses surfactant | Reporting 28-day and 1-y follow up of randomized, double-blind, placebo-controlled study | 700-1,100 g; 1 vs 3 doses prophylactic | 3 doses led to decreased severity of RDS; morbidity and mortality rate comparable to 1 dose | Corbet, 1995[49] |
| Exosurf | Of 1,046 original n, 735 were alive, and 597 had follow up | 1-y follow up of patients from 3 randomized, placebo-controlled studies | 500-1,350 g, prophylactic, single dose | Reduced mortality without increasing health, growth, or neurodevelopmental impairment | Corbet, 1995[50] |
| Exosurf | 385 original;<br>258 evaluated at 1 y;<br>118 evaluated at 2 y | Reporting 1 and 2-y follow up of patients from randomized, double-blind, placebo-controlled study | 700-1,350 g prophylactic single dose | No health, growth, or neurodevelopmental impairment at 1 or 2 years | Kraybill, 1995[54] |
| Exosurf | Of 446 original n, 273 had 1-y follow up:<br>125 controls,<br>148 surfactant | Reporting 1-y follow up of patients from randomized, double-blind, placebo-controlled study | 700-1,100 g prophylactic single-dose | Decreased mortality and rate of asthma with surfactant; no health, growth, or neurodevelopment impairment | Sell, 1995[55] |
| Exosurf | Of 215 original n (109 control, 106 surfactant), 80 alive at 1 y and 66 had follow up | Reporting 1 y follow up of patients in randomized, double-blind, placebo-controlled study | 500-699 g, prophylactic, single-dose | Neurodevelopment at least equivalent to controls; decrease in mild-moderate functional impairment (7 vs 29%) | Walther, 1995[95] |
| ALEC | 114 control<br>117 surfactant | 9-18 mo follow up of patients from randomized, placebo-controlled study | 23-34 weeks gestation | In <30 week gestation, increased survival without impairment (57 vs 41%); decreased mortality (36 vs 67%) | Morley, 1990[45] |

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*RDS, respiratory distress syndrome

Table 10. Studies of Exogenous Surfactant Therapy in Adult Humans

| Surfactant | Patients | Study Type | Administration Method | Findings | First Author, Year |
|---|---|---|---|---|---|
| Exosurf | 51 sepsis ARDS* | Prospective, randomized, placebo-controlled study—2:1:2:1 blocked to receive 12 h/d surfactant or placebo or 24 h/d surfactant or placebo; up to 5 days | Aerosol | Safe, no significant improvement in physiology or mortality | Weg 1991,[99]<br>Weg, 1994[57] |
| Exosurf | 49 sepsis ARDS | Prospective, randomized, placebo controlled study—saline vs 40.5 mg DPPC*/mL vs 81.0 mg DPPC/mL | Aerosol | Safe; may improve mortality | Wiedemann, 1992[56] |
| Exosurf | 498 sepsis ARDS | Prospective, randomized, placebo controlled study | Aerosol | No change in mortality (≈41%) | Anzueto, 1994[100] |
| Survanta | 43 ARDS sepsis, trauma, aspiration, blood transfusions | Prospective, randomized—standard therapy vs 3 doses (50 mg PL*/kg × 8 doses, 100 mg/kg × 4 doses, 100 mg/kg × 8 doses) | Instilled | Decreased mortality and ventilatory needs; improved oxygenation | Gregory, 1994[63,101] |
| Curosurf | 6 ARDS (3 sepsis, 2 pancreatitis, 1 trauma) | Prospective, crossover; 4g drug in 50 mL diluent | Instilled via bronchoscopy | No change in compliance or ABG* | Spragg, 1994[102] |
| Exosurf | One man (age 50 y) on ECMO* | Compassionate use; 7.3 g DPPC (540 mL ≈ 100 mg/kg) | Instilled via endotracheal tube | Increased $P_{aO_2}$ | Heikinheimo, 1994[98] |
| Surfactant TA | 2 ARDS (1 severe burn, 1 pneumonia) | Compassionate use; 240 mg/dose; #1 had ≈20 daily doses; #2 had 3 doses | Instilled via endotracheal tube | No allergic reactions; well tolerated | Nosaka, 1990[97] |
| Curosurf | 3 ARDS (1 aspiration pneumonia, 1 sepsis, 1 pancreatitis) | Prospective, crossover; 4 g (≈50 mg/kg) | Instilled via bronchoscopy | Transient $P_{aO_2}$ increase in 2 patients, dramatic and sustained increased $P_{aO_2}$ in another; no change in compliance or FRC* | Richman, 1989[96] |
| Unspecified surfactant | 1 terminally ill 4-year-old, sepsis ARDS | Compassionate use; 300 mg PL/kg | Instilled | Improved $P_{aO_2}$ and $P_{aCO_2}$ | Lachmann, 1989[66] |

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*ARDS, acute respiratory distress syndrome; DPPC, dipalmitoylphosphatidylcholine; PL, phospholipid; ABG, arterial blood-gas values; ECMO, extracorporeal membrane oxygenation; FRC, functional residual capacity.

colleagues [96] reported the use of instilled Curosurf in 3 adult patients with ARDS due to sepsis, pancreatitis, and aspiration. They were treated in a crossover sequence with a total of 4 g of surfactant delivered in aliquots to each lung lobe via bronchoscopy and with an equal volume of saline or air. Two patients had transient increases in $P_{aO_2}$ that returned to baseline within one hour, whereas the third had a more dramatic improvement that lasted 3 days. No change in compliance or FRC was noted. Placebo resulted in an initial decrease in $P_{aO_2}$ that returned to baseline within 1 hour. In a 1989 summary of the results of 4 ARDS animal models and surfactant replacement therapy, Lachmann[66] also reported instilling 300 mg/kg lipid into the lungs of a 4-year-old child with sepsis-induced ARDS. A dramatic improvement in $P_{aO_2}$ (from 19 torr to 240 torr) and $P_{aCO_2}$ (from 68 torr to 45 torr) occurred within 4 hours of surfactant administration.

In 1990, Nosaka and colleagues [97] reported the results of administering Surfactant-TA to 2 patients with ARDS—one due to severe burns and the other to postoperative pneumonia. Each patient received 240 mg surfactant/dose via the endotracheal tube. The first patient received doses on Days 4, 5, 13, 14, 22 and almost daily from Day 24 through Day 38. The second patient received 3 daily doses. Both patients tolerated the therapy well, without allergic reaction to the natural surfactant. Heikinheimo and colleagues[98] reported in 1994 the use of Exosurf in a 50-year-old patient with noncardiogenic pulmonary edema who, in spite of extracorporeal membrane oxygenation, was unable to maintain a $P_{aO_2} > 60$ torr. He was given two 270-mL doses of instilled surfactant via a side arm connector on the endotracheal tube. The doses were separated by approximately 3 hours, and each dose was delivered over a 15-minute period. The total 540 mL dose equated to 7.23 g DPPC, or 104 mg/kg. The $F_{IO_2}$ was able to be reduced from 0.90 to 0.50 within 24 hours, and ultimately the patient was discharged from the hospital.

The first randomized placebo-controlled adult study involved aerosolizing a synthetic surfactant. Weg and colleagues[57,99] have studied 4 dosing schedules of Exosurf in 51 patients with sepsis-induced ARDS. The patients were randomized in a 2:1:2:1 balanced block to receive either 12 h/day surfactant, 12 h/day placebo (0.6% NaCl), 24 h/day surfactant, or 24 h/day placebo. The concentration of surfactant was 13.5 mg DPPC/mL and patients received up to 5 days of therapy. Data from both placebo groups were pooled for analysis leaving a 3-group comparison of 17 patients/group. The primary objective of this study was to establish safety. However, measures of efficacy were examined as well. Patients tolerated the 12 and 24 h/day administration of the surfactant and placebo aerosols. The average (SD) total volume of surfactant aerosolized was 568 (53) g in the 12-h/day group and 1,128 (99) g in the 24-h/day group—the equivalent of 21.9 and 43.5 mg DPPC $\cdot$ kg$^{-1}$ $\cdot$ day$^{-1}$. The only related adverse event was one pneumothorax in the 12-h/day surfactant group, which was most likely due to a partially obstructed ventilator exhalation filter. Although the 30-day mortality decreased in a rank order from 47%, 41%, and 35% in the placebo, 12-h/day-surfactant, and 24-h/day-surfactant groups, the number of patients in each group was not large enough to achieve significance. Only 3 patients (1 placebo, 2 surfactant) died from respiratory failure, and all other deaths were related to multiple organ failure or overwhelming sepsis with cardiovascular collapse. The authors hypothesized that greater improvement might be achieved with a higher dose of surfactant.

As a follow up to the Weg et al study, Wiedemann and colleagues[56] reported use of a higher dose of aerosolized Exosurf in 49 patients with ARDS. Patients were randomized to receive placebo (0.6% NaCl, n = 16), 40.5 mg DPPC/mL (n = 16), or 81 mg DPPC/mL (n = 17). All patients received their assigned dose continuously, 24 h/day, for up to 5 days. Results showed a trend toward a reduced 14-day mortality with Exosurf (control = 50%, 40.5 mg DPPC/mL = 25%, 81.0 mg DPPC/mL = 35%). Improvements in oxygenation indices were also noted. Three adverse events were observed: 1 skin rash and 2 patients with increasing airway pressure related to partially obstructed ventilator expiratory filters.

Following the Wiedemann study, an international, multicenter, prospective, placebo-controlled, double-blind study of 725 patients with sepsis-induced ARDS was conducted. Anzueto and colleagues[100] reported the preliminary results of the first 498 patients and later reported the entire series. Patients received either placebo (0.45% NaCl) or Exosurf (13.5 mg DPPC/mL) nebulized continuously for up to 5 days. Patients were stratified by risk of mortality (APACHE III). There were no differences in 30-day mortality between groups—41% in the treatment and study groups in the preliminary report and 40% in both groups of all 725 patients. No differences in APACHE-III scores, cause of death, time of onset and severity of ARDS, documented sepsis, or underlying disease were reported. There was also no difference in physiologic indices of oxygenation and ventilation, duration of mechanical ventilation, or intensive care unit stay.

Gregory and colleagues[63,101] published two abstracts reporting the results of instilling Survanta into 43 patients with ARDS of multiple etiologies. Three dosing strategies were compared to standard therapy (control group, n = 16). Patients were given either 50 mg phospholipid (PL) $\cdot$ kg$^{-1}$ $\cdot$ dose$^{-1}$ for a maximum of 8 doses (n = 8), 100 mg PL $\cdot$ kg$^{-1}$ $\cdot$ dose$^{-1}$ for 4 doses (n = 16), or 100 mg PL $\cdot$ kg$^{-1}$ $\cdot$ dose$^{-1}$ for 8 doses (n = 19). After the initial dose, patients meeting retreatment criteria were given a supplemental dose every 6 hours until the maximum dose limit in their respective treatment group was reached. BAL was performed at baseline and at 120 hours after the first dose was given. Mortality was significantly reduced in the 100 mg PL/kg, 4-dose group (17.6% vs 43.8% for standard therapy), but a nonsignificant reduction was seen in the 100 mg PL/kg, 8-dose group (mortality, 21.1%); the latter had the maximum improvement in functional surfactant activity, as evidenced by an increase in phospholipid pool size, PC, SP-A, SP-B, a reduction in minimum surface tension, the maximum improvement in oxygenation, and minimum ventilatory requirements.

Spragg and colleagues[102] recently reported use of Curosurf in 6 patients with ARDS using a crossover design. Patients were randomly assigned to initially receive either placebo (0.9% NaCl in one patient, air in the other 5) or a single dose of surfactant (4 g in 50 mL diluent). Within 48 hours of the diagnosis of ARDS, surfactant was administered via bronchoscopy in equal aliquots to each lobar bronchus. BAL was performed prior to initial drug administration and at 4 hours, just prior to administering the alternate therapy. BAL was performed again 24 hours after initial therapy. There was a larger increase in $P_{aO_2}$ for the surfactant group (49 torr) versus controls (9 torr), although the improvement lasted less than 2 hours in 83% of the patients and less than 5 minutes in 50% of the patients. BAL results did not suggest any change in the inflammatory process, but the level of phospholipids 3 hours after instillation was increased. One patient died, and the duration of mechanical ventilation was > 30 days in 3 of the remaining 5 survivors. Lack of a more substantial surfactant response was thought to be partially related to the relatively low dose—approximately 50-60 mg/kg. Other than for Exosurf, which uses 67.5 mg DPPC $\cdot$ kg$^{-1}$ dose$^{-1}$, most exogenous surfactants are administered to neonates with RDS in doses of at least 100 mg DPPC/kg for optimal improvement.

## Dose and Delivery Issues

### Neonates

The method used to administer exogenous surfactant consists almost exclusively of instilling approximately 3-5 mL/kg surfactant while rotating the infant to optimize alveolar distribution.[103] Exosurf usually is administered through a side port on the endotracheal tube adapter while the infant continues to receive mechanical breaths, whereas Survanta is instilled as a bolus while mechanical ventilation is interrupted. Instilling the exogenous surfactant just prior to the first breath of life has been shown to improve surfactant distribution.[104] However, most neonates require tracheal suctioning at birth, which may remove the administered surfactant. In addition, the exogenous surfactant is given before the infant can be assessed for respiratory distress and may be unnecessary.[59,88] A meta-analysis by Hennes and colleagues [88] did not discern a therapeutic difference between surfactant given with the first breath and that given within the first few hours of life. The OSIRIS (Open Study of Infants at High Risk of or with Respiratory Insufficiency) trial of Exosurf suggests that early administration to high risk infants reduces mortality and chronic lung disease and that approximately 25% of the infants who were given prophylactic surfactant received it unnecessarily.[59]

When exogenous surfactant is administered after the first breath of life, the small volume of surfactant is not evenly distributed throughout the lungs.[104] Increasing the instilled volume improves the lung distribution pattern and is associated with clinical improvement in animal models.[105,106] Van der Bleek and colleagues[106] demonstrated, in an adult rabbit model, that increasing the volume instilled from 2.2 mL/kg to 16 mL/kg, with a constant dose of 100 mg/kg surfactant. Gilliard and colleagues[105] randomly varied volume (5 or 50 mL) and dose (50 or 160 mg) in normal and oleic-acid-injured lungs of adult rabbits (mean weight of 3.4 kg). In the normal lungs, the larger volume (15 mL/kg vs 1.5 mL/kg) resulted in better distribution; the concentration had no effect. Lung injury resulted in a fairly even distribution with both the low and high volume; it was speculated that lung edema fluid in the airways may facilitate distribution of exogenous surfactant, as in neonates receiving exogenous surfactant with their first breath. This was also confirmed by O'Brodovich and colleagues[107] who found that $P_{aO_2}$ rapidly increased after 50 mg lipid/kg was instilled into lungs containing large amounts (20 mL/kg) of normal saline (NS, 0.9% NaCl). It is possible that the NS acts as an enormous hypophase to which the exogenous surfactant adsorbs and rapidly spreads throughout the lung.

### Adults

In adults, instilling 2-16 mL/kg of exogenous surfactant (150-1,100 mL solution) may worsen hypoxemia until the fluid is absorbed. An alternate method of administration is to nebulize the surfactant. Table 11 summarizes some of the advantages and disadvantages of instilling versus nebulizing exogenous surfactant. Initial studies by Lewis and colleagues[108] demonstrated that nebulization was superior to the direct instillation method in treating preterm lambs with Survanta and in adult rabbits with NNNMU-induced lung injury,[109] even though only 2 or 5 mg lipid/kg reached the lung when nebulized versus 50 or 100 mg lipid/kg when instilled into the lambs or rabbits, respectively.

The underlying pattern of lung injury can influence surfactant distribution and its physiologic effect. A uniform lung-injury pattern created by total lung lavage of adult sheep was compared with a nonuniform lung-injury pattern created by protecting the right upper lobe (RUL) during lavage.[110] The animals then received either nebulized saline or Survanta for 3 hours. The distribution pattern was similar for saline and surfactant. However, a greater percentage of aerosol particles was deposited in the protected RUL lobe—50% versus 20% of particles in the RUL of the uniform lung-injury pattern. This preferential deposition of nebulized surfactant to uninjured lobe blunted the physiologic response to therapy. Similar to other nebulization studies, approximately 2.5 mg lipid/kg was recovered from the lung tissue.

In another study of a nonuniform lung-injury pattern in adult sheep by Lewis and colleagues,[111] all animals received total lung lavage followed by HCl instillation into the right mid-

Table 11. Advantages and Disadvantages of the Two Most Common Methods of Exogenous Surfactant Administration

| Method | Advantages | Disadvantages |
|---|---|---|
| Instillation | Administer large quantities over short period<br>Minimal drug wasted<br>Able to dispense into desired lobe via bronchoscope<br>Better delivery to injured lung regions in cases of nonuniform injury pattern | Heterogeneous distribution<br>Potential acute ventilatory impairment due to airway obstruction, especially with large volume |
| Nebulization | Equivalent result possible with smaller dose<br>Optimal distribution in uniformly injured lungs<br>Uninterrupted ventilation during administration<br>Well tolerated by patients | Normal lung units receive relatively more surfactant than injured areas<br>Inefficient (only 2-5% deposits into the lung)<br>Potential obstruction of ventilator expiratory filter |

dle lobe (RML) and the lingula. The animals were treated with either nebulized surfactant (Survanta) or NS for 3 hours or with instilled surfactant. The sheep given nebulized surfactant had improved oxygenation, lower $P_{aCO_2}$, and lower peak inspiratory pressures, whereas the instilled animals had a significant increase in $P_{aCO_2}$ 15 minutes after instillation. Approximately 8% of the total aerosolized surfactant dose was recovered from the severely injured RML and lingula; however about 50% of the instilled dose was recovered from these areas. The total calculated lipid recovered from lung tissue was approximately 4.2 mg/kg for the nebulized group versus approximately 63 mg/kg for the instilled group. These 4 studies[108-111] demonstrate that nebulized surfactant can produce a favorable physiologic response with only a fraction of the dose reaching the lung tissue. They also demonstrate that a major disadvantage of nebulization is the preferential deposition of aerosol particles into the normal, well-ventilated lung segments rather than into those that are more severely injured.

In several adult human studies, nebulizers were used to administer surfactant. Two adult synthetic surfactant studies already described [56,57] used a special nebulizer that is activated by electronic connection to the ventilator. An early version of this Vortran Intermittent Signal Activated Nebulizer, (VISAN-8 [VN-8/VI-4], Vortran Medical Technology Inc, Sacramento CA) initiates nebulization at the beginning of the inspiratory cycle and provides flow to deliver one half the $V_T$, with the remainder delivered by the ventilator.[112,113] The nebulizer produces respirable particles with a mass median aerosol diameter of 2 to 3.5 $\mu$m, depending on operating conditions. Its maximum aerosol output is stated to be 36.6 $\mu$L/L carrier gas at a nozzle pressure of 30 psi, with the concentration decreasing as pressure is either increased or decreased.[112] Up to three jets can be used to maximize flow and output. Improvements were made to this model, resulting in the VISAN-9.[114,115] The VISAN-9 nebulizes during the expiratory phase, filling the inspiratory limb of the breathing circuit with aerosol as the patient expires so that the next inspiration is charged with surfactant particles. This method allows for a larger volume of aerosol to be delivered with each breath, such that approximately 75% of the $V_T$ contains aerosol.

A major equipment concern when surfactant is nebulized through ventilators is the risk of occluding expiratory-limb filters. As noted previously,[56,57] filters can become occluded resulting in a cascade of adverse events (eg, barotrauma, hemodynamic sequelae, and possibly death). To protect the ventilator filter a commercially available, heated expiratory filter (Star Exhalation Isolation System, Infrasonics, San Diego CA) has been used as a prefilter. A bench evaluation[113] demonstrated a prefilter life of approximately 7 hours (range 5.3-9.0 h). However, the prefilter was changed at 4-hour intervals during the clinical trials to provide an extra margin of safety. In spite of this precaution, partial prefilter occlusion occurred.

The VISAN-9 nebulizer measures resistance to flow and monitors filter obstruction.[114] It alarms when a resistance equivalent to 4 cm $H_2O \cdot min \cdot 100\ L^{-1}$ is sensed. An unheated aerosol filter (Millipore Corp, Bedford MA) was produced that was effective for 11-13 hours before the VISAN-9 filter alarm sounded; when changed at this frequency, it protected the ventilator filter for at least 48 hours.[116] This nebulizer proved to be much easier and safer than the VISAN-8 and was used in the subsequent adult study.[100] In spite of increased ease of use and safety, caution must still be maintained, especially when the nebulizer is used with a patient whose compliance is improving. A bench study has determined that activation of the nebulizer during expiration causes a slight increase in mean (SD) peak inspiratory pressure [2.7 (2.2)%], $V_T$ [3.3 (2.1)%], and PEEP [0.7 (0.5) cm $H_2O$]; a modest increase in the actual time to fully exhale [22.3 (7.5)%]; and slight reduction in peak expiratory flow [7.0 (6.8)%].[117] These effects, which were exaggerated by increasing compliance and by manipulations that decreased expiratory time, may lead to the development of air-trapping. Monitoring peak expiratory flow may provide an early indication of filter occlusion,[118] and waveform graphics can help detect the lengthened time to fully exhale and resultant air-trapping.

## Concluding Remarks

With the favorable response in neonates with RDS, the positive results of animal studies, and the encouraging trends in small adult trials, why did synthetic surfactant therapy not prove successful in the large ARDS trial? There are at least five possible reasons. First, the delivered dose may have been too small. Infants are normally given 67.5 mg of DPPC/kg of instilled Exosurf. Anzueto et al[100] nebulized a concentration of 13.5 mg DPPC/mL for up to 120 hours. The VISAN-9 nebulizer aerosolizes approximately 40 g/h[114] (or 40 mL/h) and about 4.5% of the particles delivered are deposited to the lungs.[119] This calculates to a maximum 5-day total dose of approximately 42 mg/kg for a 70-kg person or 8.4 mg DPPC $\cdot$ kg$^{-1}$ $\cdot$ day$^{-1}$. Second, the surfactant preparation itself may not be optimal. Although Exosurf has proven effective in neonates, it has not performed as well as other preparations in most comparisons of functionality. More comparisons of the various surfactant agents with each other are needed to help identify the ideal agent. The next generation of exogenous surfactant agents will probably be based on synthetic hydrophobic polypeptides, mimicking the structural and biophysical properties of SP-B and SP-C.[120] Third, the ideal delivery method has yet to be determined. Although nebulization offers many advantages (Table 11), it does not promote deposition in the diseased regions of a lung that has sustained a nonuniform injury. It is possible that a combination of instilling surfactant into the affected areas and nebulization may have a role in adult surfactant delivery.[110] Fourth, timing of the initial dose, in relation to the disease process may be important. It is possible that the sepsis patients in the three cited studies[56,57,100] were given the initial dose of synthetic surfactant too late in the disease course and that too much damage had already occurred to the pulmonary surfactant system. Fifth, the disease process itself could be a factor. It may be that sepsis-induced ARDS cannot have a strong response to surfactant replacement therapy. ARDS is a surfactant-deficient condition, but in sepsis the surfactant abnormalities are likely secondary to the inflammatory response to mediators and not the primary cause of the ARDS. It is possible that ARDS of other etiologies may respond more favorably to surfactant therapy.

In summary, evidence that lung injury is related to surfactant dysfunction exists. Although exogenous surfactant has proven beneficial for neonates with RDS, it has not proven beneficial in adults with ARDS. Further research is needed to determine the ideal preparation, dose, delivery method, optimal timing of administration, and specific disease processes in which it may be beneficial.

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## Haas Discussion

**Hurst**: I'll break the ice. One of the things that has always concerned me about administering a compound that had to be aerosolized with a particle size less than ideal is particle distribution. You know it is going to be distributed to those parts of the lung that are well aerated and not to the parts of the lung that probably really need the drug. That likewise brings up a very interesting point: the timing of the administration in adult sepsis-induced ARDS. I think any of these compounds that require aerosolization, (with the exception, perhaps, of the hydrocarbons that we're going to talk about momentarily) they are going to have to be introduced when the patient is at risk for development of ARDS, prior to the time it is developed. I'm sure Rich (Branson) will remember a surgical resident, Steve Tennenburg, in Cincinnati who was looking at radioactive phosphorous lung scans to try to select out a group of patients who were at risk for ARDS after their insult. Treatment was based on this predictive scan. The problem was that the molecule was too small. Pore size in the lung readily allowed passage of the compound, particularly in smokers and patients with pre-existing lung disease, to the point they had abnormal lung scans. As a baseline, I think the technical challenge to all of us is to be able to predict when patients are going to be at greatest risk. We certainly have a treatment window to use compounds like this, and potentially others, but I think we're using it too late.

**Slutsky**: I agree with you, Jim. Studies looking at various cytokines show that quite early on, you can predict which patients are going to go on to develop ARDS with a reasonable probability. For this study[1], trauma patients were admitted and had a mini lavage. They didn't necessarily have any evidence of lung injury, but an elevated interleukin-8 (IL-8) predicted quite well which ones were going to go on to develop ARDS. The other problem from the data you presented is that Exosurf was studied the most. When you presented all the animal data and all the in vitro data, it seemed like that was the worst surfactant to use, wasn't it? I mean, you could almost predict from the animal studies that it wouldn't work. It's unfortunate that what is perhaps one of the worst surfactants was used for that large trial.

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**Haas**: I think that the rationale to conduct the large adult trial was based on the fact that (1) Exosurf had proven to be so effective with neonates, and (2) the initial studies that were reported by Weg et al[1] and Weidemann et al[2] appeared to show improved mortality.

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**Kacmarek**: As a general question to everybody, considering the varying etiology of ARDS, can we really expect surfactant in adults to have any significant effect on the overall outcome of the disease as compared to what we see in neonates where you have a singular injury? Are we really chasing something that may only have a beneficial effect in an extremely small percent of adult ARDS patients who we are unable to identify yet?

**Slutsky:** There is no correct answer, Bob. The predisposing factors vary tremendously, and the pathogenesis, obviously, is different. On the other hand, if you look at the pulmonary mechanics, it's pretty hard to tell patients apart. If I showed you the pressure-volume curves and other mechanical aspects of the lung, they look pretty much the same. That's what this is supposed to treat. That the reason the mechanics are abnormal is, in fact, surfactant dysfunction in all of these cases, I'm not sure is known for certain. You can make an argument that that's a final common pathway. If it's the surfactant dysfunction that's causing the change in mechanics, and if you then ventilate and worsen the injury, then maybe you could have an impact with exogenous surfactant, even if there are diverse etiologies for ARDS. It's clearly easier in neonates. Not only is there a common disease process, but you know exactly the time that the disease starts. That's a problem in adults.

**Branson**: Carl, is the manufacturer going to pursue bronchoscopic instillation, perhaps, with Exosurf? I have always felt the biggest problem with that entire study was delivering it through that aerosol system, which turned out to be more trouble than it was worth. It might have been more useful to put somebody on some kind of lateral rotation and then just instill it every 4 hours with a bronchoscope. I don't know—maybe the other preparations are going that way.

**Haas**: I'm not aware of any future plans for adult studies using Exosurf.

**Hurst**: At the last investigators' meeting a year or so ago, study results were released. Unless something has changed since then, they had no intention of pursuing it any further, at least in adults.

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# Liquid Breathing—Partial Liquid Ventilation

James M Hurst MD and Richard D Branson RRT

**Introduction**
**Early Evidence on Liquid Ventilation**
**The Nature of Perfluorocarbons**
**Tidal Liquid Ventilation**
**Partial Liquid Ventilation**
**Recent Studies on Liquid Ventilation**
**In Summary**

## Introduction

Despite advances in our understanding and in technology, acute respiratory distress syndrome (ARDS) continues to be a complex entity that taxes the skills and resourcefulness of clinicians worldwide. The evolution of mechanical ventilation techniques, many of which have been eloquently described during this Conference, has rekindled an interest in methods that are unique—ie, very different from traditional therapy. One such method is liquid breathing.

The concept of liquid breathing is an old one. At the University of Cincinnati and Cincinnati Children's Hospital during the 1960s, Leland Clark and his co-workers studied the possibility of liquid breathing in animals. More recently, liquid ventilation has been applied in adults and children in limited studies.

Liquid breathing is typically separated into two categories, tidal or total liquid ventilation (TLV) and partial liquid ventilation (PLV) also referred to as perfluorocarbon-associated gas exchange (PAGE). With both techniques, the lung is filled to functional residual capacity (FRC) with perfluorocarbon. With TLV, tidal volume ($V_T$) is also liquid and requires a special ventilator; it is the more experimental of the two techniques. $V_T$ during PLV is breathing gas, and a conventional gas ventilator is used to deliver the $V_T$. The liquid portion of ventilation can be considered 'liquid PEEP' (positive end-expiratory pressure) because gas exchange between the atmosphere and the alveoli (oxygen delivery and carbon dioxide removal) continues to be accomplished by gas ventilation.

## Early Evidence on Liquid Ventilation

Early efforts by Kylstra et al[1] showed that a canine model could be ventilated using hyperbarically oxygenated normal saline (NS, 0.9% NaCl). Although this technique was successful over the short term, it suffered several shortcomings. The main shortcoming was the low solubility of oxygen in NS (2 mL $O_2$/100 mL NS), making oxygen transfer to the alveoli inefficient. Another shortcoming was the viscosity of NS. Ventilating a lung with gas requires attention to time constants and the ratio of inspiratory to expiratory time. These factors are magnified 10-fold during TLV. Movement of a liquid in and out of the numerous bifurcations of the narrow tracheobronchial tree requires prolonged inspiratory time and expiratory time. Maximum respiratory frequency during TLV is typically < 8 breaths/min. Finally, surfactant is soluble in NS. Hypercapnia and hypoxemia resulting from surfactant washout proved to be technical problems that could not be overcome when NS was used. Of interest is that researchers today commonly use surfactant washout with NS in animals to produce a model of ARDS.

In 1966, Clark and Gollan[2] demonstrated that mice could be successfully supported while submerged in an oxygenated

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perfluorocarbon. This historic study launched research into liquid breathing techniques by professionals with such diverse interests as hyperbaric and aerospace medicine, hypo- and hyperthermia, developmental physiology, and lung mechanics. Clark was famous for holding a mouse under perfluorocarbon for visitors to his lab and watching the guests marvel as the animal thrived.

### The Nature of Perfluorocarbons

Perfluorocarbon liquids are a class of compounds with properties ideally suited for liquid breathing.[3] Perfluorocarbons have high gas solubilities (50 mL $O_2$/100 mL perfluorocarbon in 100% $O_2$ at 1 atm). The viscosity of perfluorocarbons is somewhat less than water, and the surface tension (14-20 dyn/cm) is very low, about 20-25% that of NS. Perfluorocarbons are also biologically inert, nonabsorbable, and, most importantly, immiscible with native or exogenous surfactant. Like NS, perfluorocarbon liquids decrease the alveolar gas-liquid interface, thereby improving alveolar compliance. Because the process improves ventilation and because the carrier liquid—perfluorocarbon—is immiscible with surfactant, perfluorocarbons can improve ventilation-perfusion matching and parenchymal compliance.

Currently available commercial products are produced by an electrochemical process; the organic compound is electrolyzed with anhydrous hydrofluoric acid. This lends thermal stability to the molecule at temperatures up to 400° C. The boiling points of perfluorocarbons are much lower than those of their native organic compounds, allowing them to vaporize at body temperature and making them suitable for instillation into the tracheobronchial tree.

### Tidal Liquid Ventilation

Early studies concentrated efforts on tidal liquid ventilation to investigate the effect of both NS and perfluorocarbons on pulmonary function after brief periods of ventilation.[4-8] They reported adequate maintenance of arterial oxygen tensions; however, progressive respiratory acidosis that was reversed after return to gas breathing was observed. Another interesting observation following the return to gas breathing was a decrease in pulmonary compliance that persisted for approximately 24 hours. Surviving animals were followed for up to 1 year after treatment and, at the time of sacrifice, were found to have essentially normal lung function. These investigators also observed that residual perfluorocarbon remained within the normal lung for at least 1 year after treatment. Other researchers have observed residual perfluorocarbon in trace amounts for as long as 2 years after treatment.[9]

Other studies combined synthetic fluids consisting of perfluorocarbons and polysiloxane to support air-breathing mammals.[7] Varying degrees of pulmonary pathology were seen in many of these animals, and those in which pulmonary changes were most severe did not survive. These pathologic changes included focal atelectasis, leukocyte infiltration into atelectatic areas, alveolitis, bronchitis and peribronchitis, alveolar edema and hemorrhage, and perivascular edema and hemorrhage. The conclusion of these researchers was that the abnormal pathology resulted from exposure to the polysiloxane compounds rather than from exposure to the perfluorocarbons. Other interesting observations were noted in the early days of TLV—Modell et al,[10] studying a canine model, observed a thick mucoid material washing out of the lungs during the first 10 minutes of TLV. It would not be appreciated until much later that pulmonary lavage, by washing mucus and alveolar debris from the lung, might be important to restoring FRC.

Once it became obvious that TLV was possible for an extended period, researchers began to concentrate on the uptake, distribution, and excretion of these compounds from intact animals models.[11] Absence of excess perfluorocarbon in urine suggested that these compounds were neither actively metabolized nor excreted unchanged in the urine. Distribution in the intact animal depended on the lipid concentration of involved tissues.[12,13] The demonstration of vacuolated macrophages in the lungs was consistent with the observation that minute quantities of perfluorocarbon remained in the lung more than a year after the study.[9,10] The issue of increased $P_{aCO_2}$ was partially solved by ventilating animals at a rate of 4-5 breaths/min and allowing a prolonged inspiratory time (4-5 s) to account for the long time constant of perfluorocarbon liquid.[14,15]

After the mechanically assisted tidal ventilation system effectively eliminated the problem of hypercapnia, a persistent metabolic acidemia was observed during liquid breathing. This observation was subsequently attributed to a concomitant 48% decrease in cardiac output. In the absence of both hypoxemia and hypercapnia, extensive redistribution of cardiac output occurs in a normothermic system. Myocardial blood flow was observed to be decreased by as much as 36% and may account for the decrease in cardiac output. Although the mechanisms have not been completely elucidated, possible explanations include an increase in pulmonary vascular resistance of the fluid-filled lung and a decrease in coronary blood flow, resulting in myocardial ischemia—either of these could alter the contractile characteristics of the left ventricle.[16,17]

Newborn animal models of both respiratory distress syndrome and meconium aspiration comprised the next wave of research on liquid ventilation. Studies supported the early contention that this technique supported adequate ventilation in an immature newborn porcine model. In addition to the lack of an observable decrease in phospholipid synthesis, the immature, atelectatic lung, if supported, was capable of increased lecithin synthesis—necessary for lung maturity.[18]

In a lamb model of meconium aspiration, studies demonstrated that pulmonary blood flow in a liquid-filled lung was more evenly distributed than in the gas-filled lung.[19] An increase in pulmonary compliance was noted, indicative of more uniform ventilation with the elimination of the liquid-air interface. That pulmonary vascular resistance is increased during liquid ventilation was subsequently proven to be the result of the mechanical interaction of the alveolar-vascular interface during liquid ventilation.[19,20]

The major roadblock in the development of TLV remains the absence of a mechanical technology for delivering, warming, and oxygenating the perfluorocarbon. In the natural version of liquid breathing, as occurs in fish, the liquid passes over the gills under pressure and is eliminated through the operculum. This unidirectional system is ideal for liquid breathing and eliminates the concerns of resistance. However, the to-and-fro system of the human lung with its numerous bifurcations and narrow airways resists the movement of the liquid. Liquid ventilators are sure to be marvels of technology, adding a new branch to current classification schemes. However, these technical difficulties and the inherent resistance of the human lung to liquid movement relegates TLV to a purely experimental technique.

### Partial Liquid Ventilation

PLV takes advantage of the ability of the liquid-alveolar interface to improve pulmonary compliance, while eliminating the need for special ventilatory technology. During PLV, a volume of perfluorocarbon approximately equal to FRC is added to the lungs. This amount is estimated to be 30 mL/kg or about 2,400 mL in an average-size adult. Alternatively, perfluorocarbon is added until at end-expiration, in the absence of PEEP, a meniscus can be seen in the endotracheal tube. Tidal (gas) ventilation is then instituted over the 'liquid FRC.' Respiratory gas exchange occurs as gas travels along the airways directly to some alveolar units and by forming bubbles in the perfluorocarbon reservoir. Respiratory gas tensions in the perfluorocarbon and individual gas bubbles add or remove oxygen and carbon dioxide according to their respective partial-pressure differences. Under inspiratory positive pressure, the liquid is forced outward to accommodate the gas $V_T$. At end-expiration, the perfluorocarbon returns to its previous position. Because of the resistance to liquid flow, the gas exits the lung ahead of the liquid.

Another potential advantage of this technique is the liquid-PEEP effect. The low surface tension of perfluorocarbons allows equal distribution of fluid throughout the entire lung. However, liquid PEEP is preferentially applied to the dependent lung regions. For a patient in the supine position, the dorsal (most dependent) regions receive a higher level of PEEP as a consequence of the height of the liquid column within the lung. The ventral or independent regions receive a lower PEEP because they are near the top of the liquid column. Given the concern about maldistribution of inspired gases during traditional gas ventilation, the development of volutrauma from over-stretching normal alveolar units, and the propensity of gas to follow the path of least resistance (to independent, normal alveoli), PLV offers clear advantages.

Early animal studies with this technique revealed that effective gas exchange occurred with elimination of surface tension, improved pulmonary blood flow, and gas exchange in conjunction with support by conventional techniques.[21-26] PLV, in addition to being simpler to use than TLV, offers the obvious advantages of tidal gas ventilation and perfluorocarbon-maintained FRC. Assisted tidal ventilation obviates the need for the participation of alveolar air in gas exchange during expiration by purging $CO_2$ and bubble-oxygenating the perfluorocarbon reservoir. This technique also provides a medium with low surface tension to facilitate bubble formation and expansion throughout inspiration and reduces surface tension along much of the alveolar surface where the perfluorocarbon lies against the alveolar lining. Studies using PLV in animal models of both lung immaturity and ARDS have provided several key observations.[27-29]

- Distribution of gas to dependent regions of the lung is minimal during gas ventilation in the setting of respiratory failure (Fig. 1).

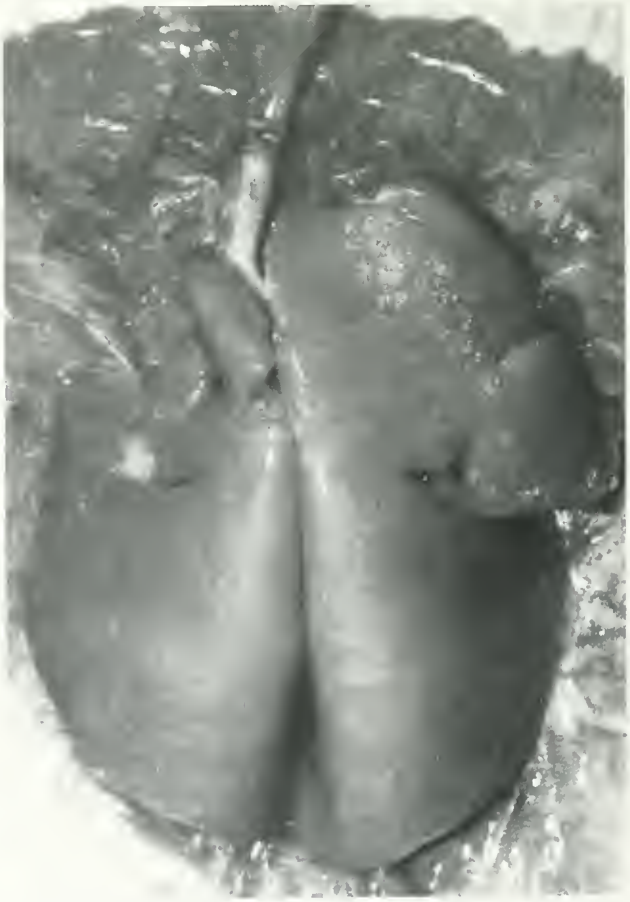

Fig 1. Excised animal lungs that had been ventilated with partial liquid ventilation. Ventilation is uniformly distributed among dependent lung units. From Reference 29, with permission.

- Distribution of the ventilating medium is more uniform in liquid ventilation when compared to gas ventilation in the setting of lung injury (Fig. 2).
- Gas exchange and pulmonary function are improved during liquid ventilation as compared to gas ventilation.
- There is histologic evidence of reduced lung injury following liquid ventilation when compared to gas ventilation (Fig. 3).

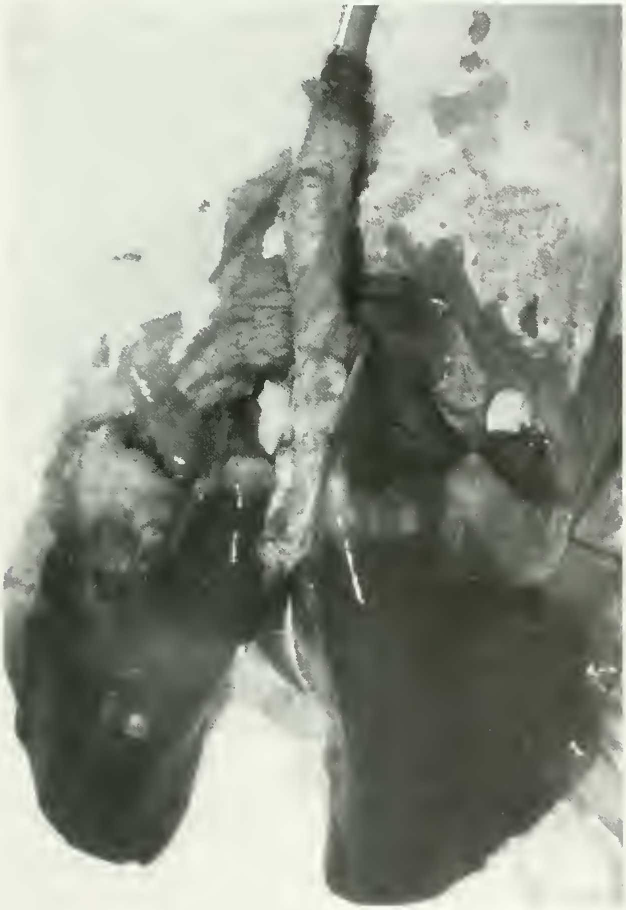

Fig. 2. Excised animal lungs that had been ventilated using pressure-control ventilation. Gas distribution is not uniform. Patchy areas of inflation/atelectasis can be seen.

Hirschl and colleagues[28] compared the CT images of an animal model of ARDS to those of patients in the clinical setting and confirmed (as had been previously shown in patients with ARDS) that atelectasis, consolidation, and accumulation of exudate occurs in the dependent regions of the lung. Ventilation with a liquid medium may improve gas distribution and result in washout of the exudate in the atelectatic regions. The marked decrease in inflammatory reaction in the regions of the lungs ventilated with the liquid medium raises interesting questions regarding the overall role of perfluorocarbons.[29] Virmani et al[30] investigated the effect of perfluorocarbon blood substitutes on human neutrophil function. Human neutrophils exposed to perfluorocarbons showed a marked inhibition of chemotactic and phagocytic responses. These effects appear to be dose dependent. Smith et al[31] investigated the production of reactive oxygen species (oxygen free radicals) by alveolar macrophages exposed to liquid perfluorocarbon chemicals. Respiratory burst activity of alveolar macrophages, as measured by hydrogen peroxide production and chemiluminescence, were markedly decreased when compared to nonexposed cells. Further studies are pending regarding the nonspecific anti-inflammatory properties of the perfluorocarbons.

## Recent Studies on Liquid Ventilation

In a small series of adult patients with ARDS[32] and in another of pediatric patients,[33] all on extracorporeal life support, PLV was associated with improvements in gas exchange and pulmonary compliance. A multicenter human trial is currently underway in the United States. A total of 60 patients have been studied. These include neonates with respiratory distress syndrome and adults and children with ARDS. Inclusion criteria for the ARDS population are bilateral pulmonary infiltrates, $P_{aO_2}/F_{IO_2}$ 75-200 ($F_{IO_2} \geq 0.5$), and pulmonary capillary wedge pressure ≤ 18 mm Hg. Exclusion criteria include a history of congestive heart failure with a pulmonary capillary wedge pressure > 18 mm Hg, chronic obstructive pulmonary disease, bilirubin ≥ 4 mg/dL, creatinine ≥ 5 mg/dL, intracranial pressure > 25 mm Hg or Glasgow Coma Scale score ≤ 8, death expected within 30 days, pregnancy and lactation, interstitial lung disease, bronchopleural fistula, and HIV infection. The initial dose is 2.5-5.0 mL/kg increasing to predicted FRC (approximately 30 mL/kg). Perfluorocarbon is 'trickled in' through a side port in the endotracheal tube connector. The administration of this initial dose requires 90-120 minutes. When a meniscus is seen in the endotracheal tube with the patient on zero PEEP, instillation is considered complete. Weaning from partial liquid ventilation is to be accomplished between 24 and 48 hours. In the Phase-I and Phase-II pilot studies, 78% of the patients had sepsis and/or pneumonia. Seventy-eight percent of all patients were alive at 28 days and 44% were alive as of April 1995. The mortality predicted by Apache-II scores[34] was 60% for this group of patients. These data are, as yet, unpublished.

## In Summary

Perfluorocarbons are an interesting family of compounds capable of providing adequate gas exchange, improvement in pulmonary compliance, and redistribution of pulmonary blood flow in both animal models and human studies of acute lung injury. Although all the mechanisms that contribute to the improvements in gas exchange have not been elucidated,

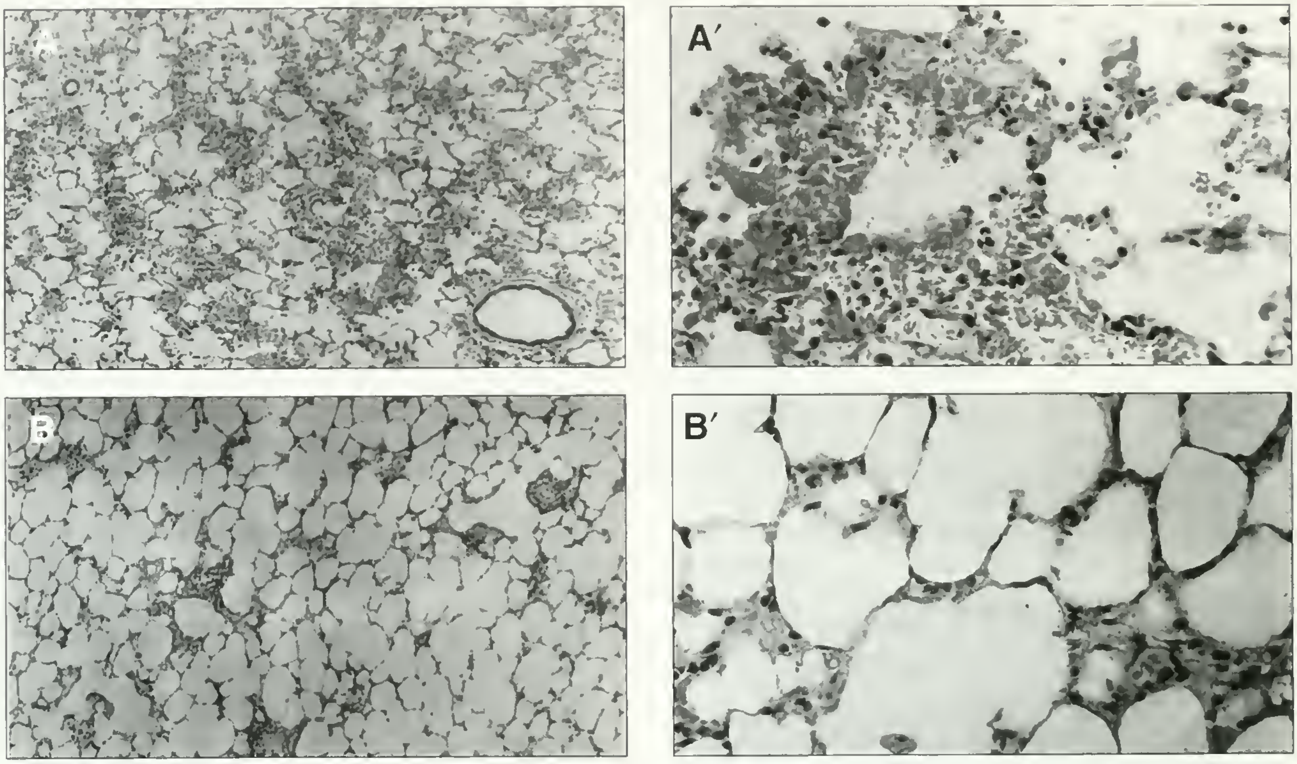

Fig. 3. Photomicrograph of lungs that have been ventilated with conventional techniques (A) and partial liquid ventilation (B). The right panels (A′, B′) are high-power magnifications of the images on the left. Both low- and high-power images of A show airway dilatation and alveolar collapse alternating with overdistention, debris in the airspaces, and thickened septa. The images of B show uniform inflation, normal airways, and normal septa.

various speculations include liquid PEEP. The gas-liquid interface in alveoli is abolished and lavaging the exudate containing pulmonary inflammatory mediators from the atelectatic alveoli restores FRC. The speculation that perfluorocarbons may actually be anti-inflammatory agents requires further study. Although the future of PLV has not been completely defined, it is clear that it will assume a prominent place in our arsenal for the treatment of patients with acute lung injury who are unresponsive to conventional therapy. Because of the current investigative nature of the technique, it is limited to tertiary referral centers. No evidence supports presumptive use of these compounds in patients at high risk for developing acute lung injury after exposure to noxious agents.

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## Hurst Discussion

**Peruzzi**: I'm impressed by the difference in pathology between the non-perfluorocarbon-ventilated lungs and the perfluorocarbon-ventilated lungs. Do you attribute the much less severe lung pathology noted with perfluorocarbon-ventilated lungs to the mechanics of avoiding alveolar overdistention, as we talked about already in this conference to some degree, or do you attribute that more to the biochemical effects, the anti-inflammatory effects of the perfluorocarbon compound? How would you go about studying it to differentiate the two mechanisms?

**Hurst:** Right now, I have to presume (I'd love to hear everybody else's comments) that it's twofold. Maintaining a lung in a partially inflated position is going to be good. Second, I think that the investigators stumbled across the anti-inflammatory properties, whether part of that is mechanical (that is, lavaging out the inflammatory cells and their mediators) and whether there's another, either local anti-inflammatory component or systemic anti-inflammatory component, I don't know. I don't know the best way to separate these out. I've talked it over with Joe Solomken in our institution. One of the things that we talked about doing was looking at the number of inflammatory mediators, both in the pulmonary artery and in lavage fluid. He seems to think, right now, that it might be an insurmountable problem. I don't know whether that's true or not. The answer is, I don't know.

**Adams:** This is a thick liquid. Could it be that the vertical column of pressure that's created reroutes blood flow from the dependent segments to the independent, better ventilated segments?

**Hurst:** I think it has been shown that there is a better redistribution of pulmonary blood flow. That's true.

**Branson:** I think it's a lot of those things. There's the column of fluid that not only redistributes pulmonary blood flow, but, like Bill and Art, and half a dozen other people have shown us in this conference, the dependent regions of the lung are the areas that are collapsed. And with gas ventilation, gas follows the path of least resistance, which is to the alveoli that are open. But, it appears as though liquid ventilation, just by virtue of the depth of the column of liquid, actually provides the most amount of pressure to the alveoli that are collapsed. So it seems to be multifactorial, obviously, like a lot of things, and it just seems ideal.

**East:** I have just been visiting with Alliance. They showed me some data and slides that would indicate that liquid is more uniformly distributed. It's not like water that just sits there. ...

**Hurst:** I think these slides taken from Alliance's video speak to that, and the video is even more impressive. I didn't bring the video because it's about 20 minutes long, but when you show the progressive instillation of these compounds, it really is distributed very nicely—not only to dependent but also to independent part of the lungs.

**Wilson:** We've actually treated three patients, two children and one adult, in our institution with this technique. All patients showed very positive response to the therapy, with the pediatric patients having the better response. The evaporation of the drug and the redosing seem very different, depending on the size of the lung. The evaporation rate for a neonate as compared to a pediatric patient as compared to an adult is very different. The ventilatory technique is really pretty important, and I don't know that we've settled on what is the best technique to recommend. A couple of things we do know is that the oxygenation of the liquid in the lung is critical. The perflubron is unoxygenated, as it's being administered. Maintaining the $P_{O_2}$ of the perflubron is very tidal volume dependent. The normal tidal volume strategies that we employ in our pediatric patients had to be modified in our second patient, in particular, to be able to maintain the oxygenation of the perflubron. At low-level dosing, as we were instilling up to an FRC volume, the surfactant effect was very dramatic. Once we got beyond the surfactant-effect, we truly got the liquid ventilation effect. We were able to observe the changes in dosing effects by monitoring compliance and pressure-volume loops. We were able to identify when to redose based on some of those data, as well as the oxygenation data.

**Hurst:** Alex, how would you like to fill their lungs full of this and flip them?

**Adams:** Unfortunately, the airways then aim downwards and some liquid would tend to drain out.

**Hurst:** Yes, but the Stryker frame could still be adjusted so that you could retain the compound in the lung by putting patients in different positions.

**Branson:** There is another study that shows the use of perflubron with surfactant actually enhances the function of surfactant. The animals treated with the combination of the two seem to be improved over those treated with just surfactant and just perflubron. There are other uses for this drug, too. Think about direct drug delivery to the lung in patients with pneumonia by using perflubron as a carrier. So, aside from its effects on improving ventilation in patients with ARDS, it may have a lot of other uses.

**Hess:** The only problem I have with that is whether anybody has shown that the drug is carried in the perflubron? Certainly the stuff that Jim showed and others have shown is that thick, viscous slop in the lungs floats up to the top and can be suctioned off. I've heard other people say this. The question I've always had is How do you know if you put a drug into it—an antibiotic, a bronchodilator, whatever it might be—that the stuff won't also float up to the top and never get into the lung where you want it to have its action?

**Branson:** Well, I don't think you can just do it yourself. I don't think you can just decide on your own that you're going to pour something in the perflubron, but I have seen some preliminary evidence that they can bind certain drugs to the perflubron, so that it actually is delivered with the molecules.

**Hurst:** It may wind up being very much like the Fluosol-DA, which is an emulsion. Some sort of an emulsifying or liposome-type material might have the drug incorporated. Then, of course, it would depend on lipid solubility. Just one word of caution about ARDS, particularly the sepsis-induced ARDS. It's really a different animal. It's not like the neonate, obviously. The patient who comes in having received 125 units of blood during a trauma resuscitation and operative procedure who doesn't have an enteric injury and has not gotten septic ARDS yet, is one type of patient, but those who wind up with septic ARDS and so much organ-function compromise are another. Much of the mortality in that group of patients, now that we've gotten to the point where we can support oxygenation and ventilation, depends on other vital-organ function.

**Wilson:** In response to the previous discussion about combining liquid ventilation with other techniques, a fair amount of laboratory investigation looks at the response of nitric oxide with PLV. We've done that in our pediatric animal model of ARDS and those data are about to be published—perhaps in the next year and a half. It is kind of unnerving to see multiple experimental agents being combined—but that combination (NO & PLV) does seem to have a positive effect. I think the pharmaceutical company is not willing to discuss it at this point because it's still unpublished and investigational, but some applications of perflubron are yet to be seen.

**Hess:** I think we really have to be careful with these things because we don't know for sure what the toxicity of nitric oxide is. We don't know for sure what the toxicity of perflubron is. When we start putting these things together, I think we could have a lot of problems. There were some abstracts at the ATS meeting this last spring that talked about combining liquid ventilation with nitric oxide. One of the questions that I asked one of the presenters was, "When you have this oxygen in the perflubron and you kind of have the oxygen molecules trapped in there, and then you trap them in there with nitric oxide, do you generate nitrogen dioxide? Has anybody looked at that, has anybody thought about it?" The response from everybody was "Well, you know, we haven't really thought about that." That concerns me, because we know that nitrogen dioxide is very toxic, and we're not sure what the toxicity of nitric oxide might be. I'm really concerned about mixing all kinds of other things, and I think Rich's point, is well taken. As our individual centers get into some of these trials, we have to resist the temptation of "Well, we have nitric oxide over here and perflubron over there, so let's just put the both of them together and maybe it'll be better than either one by itself. It may be worse than either one by itself.

**Wilson:** Some baboon data reveal endothelial changes as a result of PLV; so, the final word on some of those toxicities really isn't in yet. I think Dean is absolutely right.

**Haas:** In working with Dr Hirschl's group, I have seen several adult patients respond favorably to PLV. In some patients, it's very dramatic, but it reminds me a little of how certain adult patients responded favorably to exogenous surfactant, and how we thought that it was going to work in ARDS. It wasn't until 725 patients had been studied[1] that it was determined that it didn't work. I remember one PLV patient, in particular, who had aspirated charcoal and had a severe pneumonia. Watching the charcoal come 'to the top' to be suctioned off was fairly dramatic, and that patient did quite well.

1. Anzueto A, Baughman R, Guntupalli K, DeMaria E, Davis K, Weg J, et al. and the Exosurf® ARDS Sepsis Study Group. An international, randomized, placebo-controlled trial evaluating the safety and efficacy of aerosolized surfactant in patients with sepsis-induced ARDS (abstract). Am J Respir Crit Care Med 1994;149(4, Part 2):A567.

**Hurst:** Again, in the adult model of ARDS, it may depend on when these compounds are administered.

**Haas:** In preparing for the surfactant lecture, I considered presenting a cost projection for adult therapy, but it would have involved a lot of assuming. A neonatal dose costs about $600, give or take $50. In the adult Exosurf studies, 20 vials of a concentration of up to six times the neonatal dose were used over the 5-day period. If we assume similar pricing per vial, aerosolized Exosurf for adults would cost up to $12,000 for the drug, but it is very unlikely that a pharmaceutical company would charge that much. I assume it doesn't cost $600 to make a vial of neonatal surfactant, and I am sure that a reasonable price would have been determined for the adult dose.

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# Use of Inhaled Nitric Oxide in Patients with Acute Respiratory Distress Syndrome

Dean Hess PhD RRT, Luca Bigatello MD, Robert M Kacmarek PhD RRT, Ray Ritz BA RRT,
C Alvin Head MD RRT RPFT, and William E Hurford MD

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## Introduction

Nitric oxide (NO) is a ubiquitous, highly reactive, gaseous, diatomic molecule (Table 1). Because NO is considered an occupational and environmental pollutant, the Occupational Safety and Health Administration (OSHA) has developed limits for NO exposure in the workplace.[1] Since the mid-1980s, clinical and academic interest in NO has moved from environmental and public health to cellular biology and physiology. It is now recognized that NO is an important messenger molecule, and many cell types have shown the capacity to produce NO. The action of common nitrosovasodilators (eg,

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sodium nitroprusside and nitroglycerin) is due to their release of NO.[2,3] In 1992, NO was named Molecule of the Year by the journal *Science*,[4] and thousands of papers and abstracts are published each year on biomedical aspects of NO.

Table 1. Physical and Biochemical Properties of Nitric Oxide*

High diffusibility
High lipid solubility
Gas or solution at body temperature
Reactive free radical
Short half life (3-50 s)
Oxidized to $NO_2$ in air
Oxidized to nitrites and nitrates in solution
Activity inhibited by hemoglobin, myoglobin, methylene blue, superoxide
Activity potentiated by superoxide dismutase, cytochrome c, hydrogen ions

*Adapted from information provided in Reference 8.

There is intense clinical interest in the use of inhaled NO in the treatment of diseases characterized by pulmonary hypertension and hypoxemia (Table 2), but inhaled NO has not yet been approved by the U. S. Food and Drug Administration (FDA) for this application except as an investigative drug. However, several large multicenter randomized placebo-controlled studies are underway evaluating the safety and efficacy of inhaled NO. Over the past several years, a number of review papers have been written on the topic of inhaled NO.[5-18] In this paper, we review basic aspects of the biology of NO and focus on the use of NO in the treatment of patients with ARDS and on techniques for delivery of inhaled NO.

Table 2. Potential Clinical Uses for Inhaled Nitric Oxide*

ARDS
Persistent pulmonary hypertension of the newborn
Primary pulmonary hypertension
Pulmonary hypertension following cardiac surgery
Cardiac transplantation
Lung transplantation
Acute pulmonary embolism
COPD and chronic pulmonary fibrosis
Bronchodilation
Congenital diaphragmatic hernia
Congenital heart disease

*Based on data from References 9, 10, 13-16.

## Biology of Nitric Oxide

In 1980, endothelium was shown to be essential for the vasodilator action of acetylcholine in isolated strips of arteries,[19] and stimulation of the endothelial cells resulted in release of a substance called endothelium-derived relaxing factor (EDRF). The first paper to demonstrate NO synthesis by a mammalian cell was published in 1985.[20] In 1987, it was shown that NO accounted for the biologic activity of EDRF and that L-arginine was its precursor.[21,22] Nearly every cell type studied thus far has shown the capacity to synthesize NO.[6] Some of the functions of NO include vascular smooth muscle relaxation, airway smooth muscle relaxation, neurotransmission, bacteriostasis, tumor-cell lysis, and platelet inhibition.[7]

L-arginine is the substrate for NO synthesis in biologic systems (Fig. 1).[6-10, 23] In the presence of NO-synthase, NO is produced and L-citrulline is formed as a by-product. NO is highly lipophilic and readily diffuses across cell membranes to adjacent cells, thus serving as a local messenger molecule. NO typically diffuses from its cell of origin into a neighboring cell, where it binds with guanylate cyclase. Activation of guanylate cyclase results in the production of cyclic guanosine 3',5'-monophosphate (cGMP) from guanosine triphosphate (GTP), which produces a biologic effect within the cell (eg, smooth muscle relaxation). The time between NO production and guanylate cyclase activation is short, with a half life of < 5 s for NO in physiologic systems.[7] Inhibitors of guanylate cyclase (eg, methylene blue)[24] and inhibitors of NO-synthase decrease cGMP levels, whereas inhibitors of phosphodiesterase (eg, zaprinast)[25] increase cGMP levels.

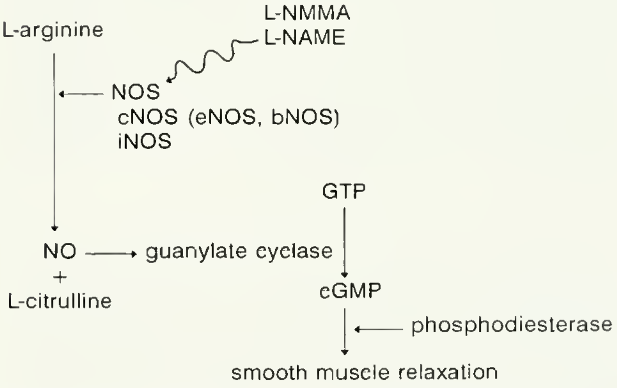

Fig. 1. Biologic pathways showing the production and activity of endogenous nitric oxide (NO). See text for term identification.

Isoforms of NO-synthase are classified either as constitutive NO-synthase (cNOS) or inducible NO-synthase (iNOS) (Table 3).[5-8,12] cNOS is always present within cells; whereas, iNOS is expressed only after induction by a number of stimuli, including cytokines, microbes, or microbial products. The two forms of cNOS are the endothelial type (eNOS) and the neuronal type (bNOS). Inhibitors of NO-synthase include L-$N^G$-monomethyl arginine (L-NMMA) and L-$N^G$-arginine methyl ester (L-NAME). Much ongoing research addresses the role of NO in endotoxemia and sepsis.[26-31] Whether inhibition of iNOS in sepsis is beneficial or detrimental is unknown.[32] Studies have shown that NO-synthase inhibitors reverse hypotension during sepsis, but the clinical benefit of this remains to be determined.

Table 3. Comparison of Constitutive (cNOS) and Inducible (iNOS) Forms of Nitric Oxide Synthase

cNOS
Cellular sources: endothelial cell, some neurons, mast cells, platelets
$Ca^{++}$-calmodulin dependent
Transiently released in small amounts
Activators: thrombin, acetylcholine, ADP and ATP, pressure and shear stress, bradykinin and histamine, leukotrienes
Function is regulation (messenger molecule)

iNOS
Cellular sources: macrophages, hepatocytes, tumor cells, endothelial cells
$Ca^{++}$-calmodulin independent
Sustained release in large amounts
Inducers: lipopolysaccharide, interleukins, tumor-necrosis factor
Inhibited by glucocorticoids
Function is host defense

NO also has cGMP-independent effects.[7] It combines with $O_2$ to form nitrogen dioxide ($NO_2$) and with superoxide ($O_2^-$) to form peroxynitrite. Nitrite ($NO_2^-$) and nitrate ($NO_3^-$) may also be produced as products of NO metabolism. NO reacts with transition metal ions and with both heme and non-heme metalloproteins. NO also reacts with a variety of other biologic metalloproteins including myoglobin and cytochrome *c* oxidase.[33] The cGMP-independent effects of NO may include bacteriostasis and tumor-cell lysis.

## NO in Exhaled Gas

It has been shown that NO is present in the exhaled gas of animals[34-37] and human beings.[38-49] Although results differ among studies (some differ by an order of magnitude or greater), most report exhaled NO < 50 parts per billion (ppb) in normal persons. Exhaled NO is increased in individuals with asthma[45-48] or bronchiectasis,[41] and decreased in individuals who are smokers[40,44,46] or hypertensive.[44] In animal models, exhaled NO is increased with sepsis[35] and the administration of positive end-expiratory pressure (PEEP),[34] sodium nitroprusside, and nitroglycerin.[36]

The origin of endogenous NO in the exhaled gas could be the upper airway, the lower airways, or the lung parenchyma. The exhaled NO could be the result of either cNOS or iNOS activity. In normal subjects, much of the NO in exhaled gas is from the upper respiratory tract. Nasopharyngeal bacteria stimulate the nasal mucosa to produce NO, and antimicrobial therapy may decrease NO production in the nasopharynx.[38] Further, it has been shown that NO levels are relatively high (≅10 ppm) in the paranasal sinuses, and it has been suggested that the bacteriostatic effects of NO may be responsible for maintaining the sterility of the sinuses.[49]

Gerlach et al[38] demonstrated an autoinhalation of NO produced in the nasopharynx and suggested that it may be important to the maintenance of the ventilation-perfusion relationship ($\dot{V}/\dot{Q}$) within the lung. They also showed that autoinhalation of NO is reduced with antibiotic therapy and with endotracheal intubation (Fig. 2). They suggested that low-dose inhaled NO (eg, 100 ppb) in ARDS patients might be considered replacement therapy because the autoinhalation of nasopharyngeal NO is eliminated by endotracheal intubation.

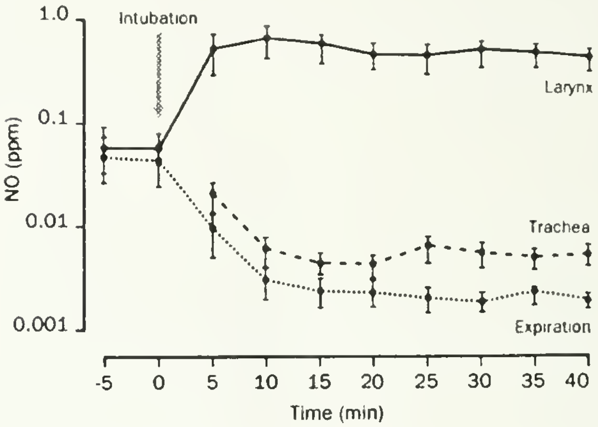

Fig. 2. NO concentrations from expiratory limb of ventilator, from trachea after intubation, and from lower oropharynx above larynx during inspiration. Note that autoinhalation of NO decreases following intubation. (Reprinted from Reference 38, with permission.)

## Selective Pulmonary Vasodilation

The term *selective pulmonary* vasodilation is used to indicate two physiologic phenomena. First, selective pulmonary vasodilators reduce pulmonary vascular resistance without affecting systemic vascular resistance. Second, a selective pulmonary vasodilator affects vascular resistance only near ventilated alveoli. Inspired vasodilators are delivered to those lung units that are ventilated. Although both low-dose aerosolized prostacyclin ($PGI_2$)[50-56] and inhaled NO have been shown to be selective pulmonary vasodilators, this review is limited to inhaled NO. It should also be mentioned that NO is not a selective pulmonary vasodilator per se, but becomes one when inhaled.

Inhaled NO selectively improves blood flow to ventilated alveoli. This has been demonstrated indirectly in human and animal studies that have shown a reduction in intrapulmonary shunt and improved arterial oxygenation, as discussed later in this paper. In animal[57-60] and human[61] studies of ARDS, an improvement in $\dot{V}/\dot{Q}$ distribution measured by multiple inert-gas-elimination technique (MIGET) has been demonstrated with NO inhalation.

It has been demonstrated in animal and human models of pulmonary hypertension that inhaled NO decreases pulmonary arterial pressure (PAP) and pulmonary vascular resistance (PVR) without affecting systemic blood pressure. In a sheep model of pulmonary hypertension (produced by intravenous infusion of the thromboxane analog U46619),[62] NO inhalation decreased PVR and PAP without affecting systemic blood pressure or systemic vascular resistance (SVR). Further, it has been shown that inhaled NO reverses hypoxic pulmonary hypertension in experimental animal[63] (Fig. 3) and human subjects[64] (Fig. 4) without systemic effects.

The selective pulmonary vasodilation demonstrated by inhaled NO is due, in large part, to the high affinity of hemoglobin for NO,[65,66] which is about $1 \times 10^6$ greater than the affinity of hemoglobin for $O_2$.[67] NO binds to hemoglobin to form nitrosylhemoglobin, which is rapidly oxidized to methemoglobin (metHb), yielding residual nitrates and nitrites.[33,67-70] The metHb is then converted to reduced hemoglobin due to the action of metHb reductase. Methemoglobinemia is a potential complication of inhaled NO therapy, as discussed later in this paper.

In contrast to inhaled NO, intravenous vasodilators (eg, sodium nitroprusside, nitroglycerin, prostacyclin) are not selective.[12,13] Although intravenous vasodilators lower PAP, they also lower SVR and blood pressure (Fig. 5). Moreover, these agents increase blood flow to both ventilated and unventilated lung units, resulting in an increased intrapulmonary shunt and a lower partial pressure for oxygen in the arterial blood ($P_{aO_2}$).

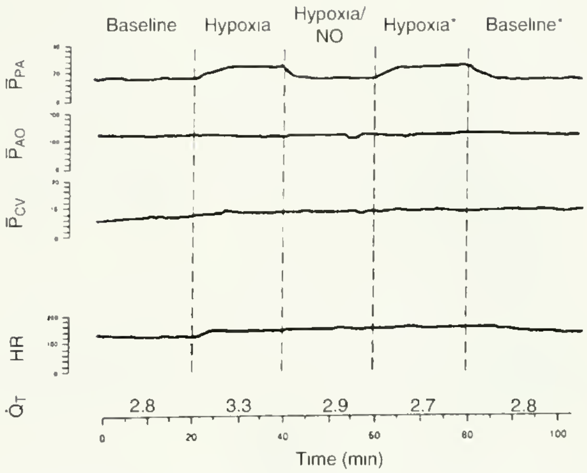

Fig. 3. Mean blood pressures [pulmonary ($\bar{P}_{PA}$) in mm Hg, aortic ($\bar{P}_{AO}$), and central venous ($\bar{P}_{CV}$)], heart rate (HR) in beats/min, and cardiac output ($\dot{Q}_T$) in L/min, in sheep ventilated with air (baseline), followed by hypoxia, hypoxia with NO, and second hypoxic gas mixture. Note the effect of inhaled NO on $\bar{P}_{PA}$ without affecting $\bar{P}_{AO}$, thus demonstrating selective pulmonary vasodilation. (Reprinted from Reference 63, with permission.)

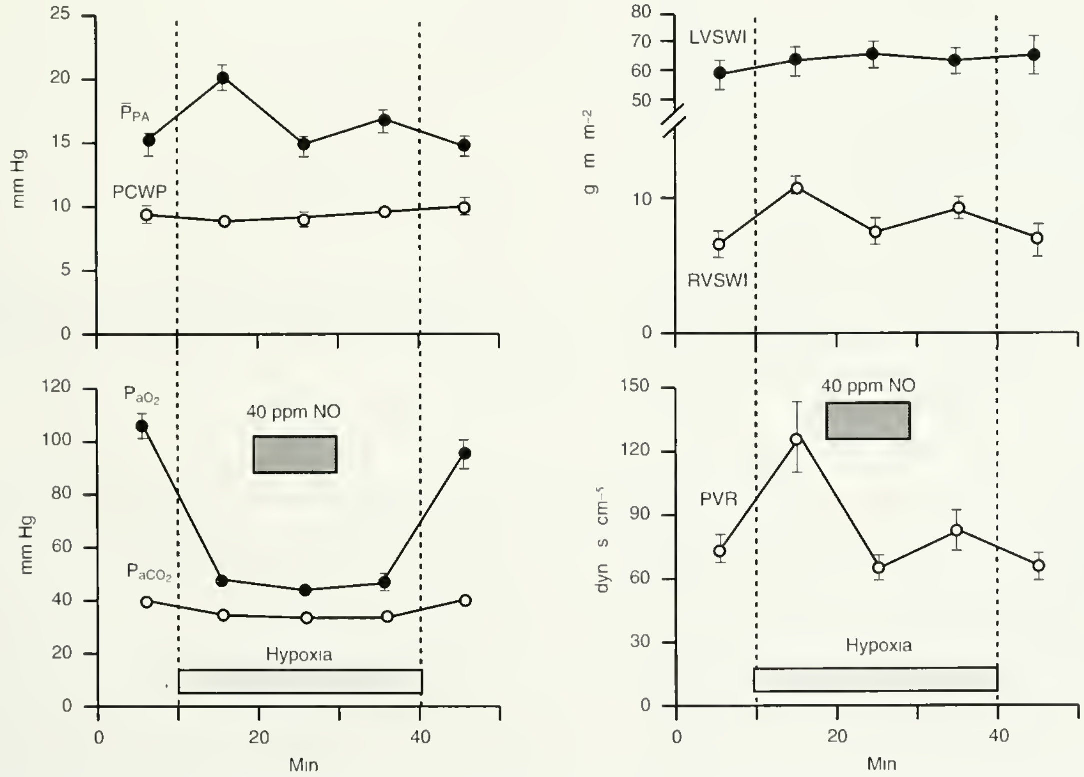

Fig. 4. Effects of inhaled NO (40 ppm) during hypoxia in 9 normal volunteers, on mean pulmonary artery ($\bar{P}_{PA}$) and mean pulmonary capillary wedge pressure (PCWP), $P_{aO_2}$, $P_{aCO_2}$, right ventricular stroke work index (RVSWI) and left ventricular stroke work index (LVSWI), and pulmonary vascular resistance (PVR). Note the effect of inhaled NO on PVR. (Reprinted from Reference 64, with permission.)

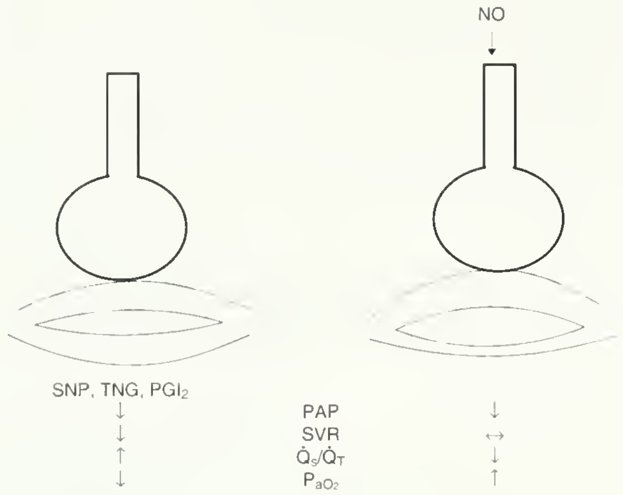

Fig. 5. Comparison of the effects of systemic vasodilators [sodium nitroprusside (SNP), nitroglycerin (TNG), prostacyclin ($PGI_2$)] and inhaled NO on pulmonary artery pressure (PAP), systemic vascular resistance (SVR), intrapulmonary shunt ($\dot{Q}_S/\dot{Q}_T$), and $P_{aO_2}$.

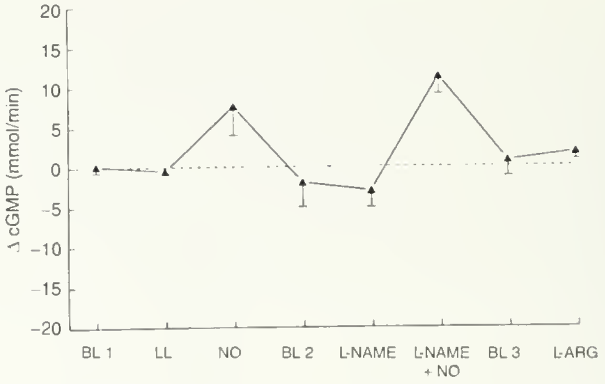

Fig. 6. cGMP release from sheep at baseline (BL 1), after lung lavage (LL), after 10 min of 60 ppm inhaled NO (NO), 10 min after ceasing NO inhalation (BL 2), after L-NAME infusion (L-NAME), again 10 min after beginning NO inhalation (L-NAME + NO), 10 min after breathing without NO (BL 3), and 10 min after L-arginine infusion (L-ARG). (Reprinted from Reference 75, with permission.)

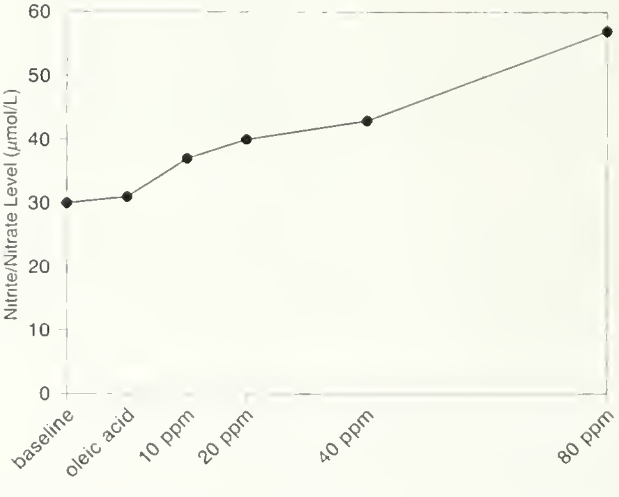

Fig. 7. Serum nitrite/nitrate levels in an animal model at baseline, after production of acute lung injury (oleic acid), and after administration of 10, 20, 40, and 80 ppm inhaled NO. (Data from Reference 76.)

## Inhaled NO for ARDS

ARDS is characterized by intrapulmonary shunting, increased dead space ventilation (ie, increased $V_D/V_T$), and pulmonary hypertension.[71] Therapy consists of supplemental $O_2$, PEEP, and high mean airway pressure. ARDS treatment is largely supportive, and mortality has changed little over the past 20 years. Moreover, therapy for ARDS ($O_2$, high airway pressure) may itself worsen the high-permeability, noncardiogenic pulmonary edema associated with ARDS.[72] There is currently (1996) much enthusiasm for the use of inhaled NO in the treatment of ARDS. Inhaled NO should produce selective pulmonary vasodilation that results in improved distribution of ventilation, less shunting, improved arterial oxygenation, and lower PVR. Although initial clinical reports are encouraging,[61,73] the role of inhaled NO in the outcome of ARDS remains unclear but may be clarified with the completion of prospective, randomized, double-blind trials.

### Animal Studies

Inhaled NO has been investigated in several animal models of ARDS (Table 4).[57-60,74-77] Most of these studies used doses higher than those now used in human clinical trials and, in general, reported an improvement in pulmonary shunt and PVR with inhaled NO. However, this effect was not found in all animals.[76] Inhaled NO was associated with an increase in circulating cGMP (Fig. 6)[75] and in nitrite and nitrate levels (Fig. 7).[70,76]

Several studies have used the MIGET to evaluate redistribution of blood flow and $\dot{V}/\dot{Q}$ with inhaled NO following lung injury.[57-60] This effect was demonstrated with oleic acid injury,[57,60] smoke inhalation injury,[58] and sepsis.[59] An interesting animal study with clinical implications was performed by Putensen et al.[60] After inducing acute lung injury with oleic acid, they found a significant interaction between continuous positive airway pressure (CPAP) and inhaled NO. Inhaled NO alone produced no significant improvement in $P_{aO_2}$ or $\dot{V}/\dot{Q}$ assessed by MIGET. However, inhaled NO resulted in an improvement in $P_{aO_2}$ following application of 10 cm $H_2O$ CPAP. The clinical implication of this may be that conventional therapy (eg, mean airway pressure, PEEP) should be maximized before the addition of inhaled NO.

Several animal studies suggest that inhaled NO may be

Table 4. Studies on Inhaled NO, Using Animal Models of ARDS (See text for term definition)

| Reference & Year of Publication | Animal Model | NO Dose Range | Physiologic Outcome Variables | Major Findings |
|---|---|---|---|---|
| Rovira et al,[75] 1994 | Ovine bilateral lung lavage; independent and combined effects of inhaled NO and infusion of L-NAME | 0 & 60 ppm | Hemodynamic & blood-gas values, plasma cGMP levels | Inhaled NO before or after L-NAME reduced shunt and PAP, most likely by increasing cGMP in ventilated lung units and causing selective pulmonary vasodilation |
| Shah et al,[76] 1994 | Porcine oleic acid; animals divided into control group (no NO) and study group (inhaled NO) | 0-80 ppm | Hemodynamic & blood-gas values, extravascular water, nitrosylated hemoglobin, methemoglobin, plasma nitrites and nitrates | Inhaled NO reversed pulmonary hypertension and intrapulmonary shunt in a dose-dependent manner; significant increases seen in methemoglobin and plasma nitrites and nitrates |
| Ogura et al,[59] 1994 | Porcine sepsis model (infusion of *Escherichia coli* lipopolysaccharide); animals divided into control group (no NO) and study group (inhaled NO) | 0 & 40 ppm | Hemodynamic & blood-gas values, multiple-inert-gas-elimination technique, wet-to-dry-lung weight after necropsy | Redistribution of blood flow from true shunt to ventilated lung units; improvement in PAP and arterial oxygenation with inhaled NO |
| Ogura et al,[58] 1994 | Ovine wood smoke inhalation | 0 & 40 ppm | Hemodynamic & blood-gas values, multiple-inert-gas-elimination technique | Modest improvement in $\dot{V}/\dot{Q}$, pulmonary vascular resistance, and arterial oxygenation with NO inhalation |
| Putensen et al,[57] 1994 | Canine oleic acid; inhaled NO with and without intravenous L-NMMA | 0 & 40 ppm | Hemodynamic & blood-gas values, multiple-inert-gas-elimination technique | Inhaled NO improved gas exchange by redistributing blood from shunt units to lung units with a nearly ideal $\dot{V}/\dot{Q}$; inhaled NO reversed the pulmonary but not systemic vasoconstriction caused by L-NMMA |
| Putensen et al,[60] 1994 | Canine oleic acid, with and without 10 cm $H_2O$ CPAP | 0 & 40 ppm | Hemodynamic & blood-gas values, multiple-inert-gas-elimination technique | Pulmonary vascular resistance lowered by inhalation of NO alone, but recruitment of gas exchange units was necessary to produce a beneficial effect of inhaled NO on $\dot{V}/\dot{Q}$ and oxygenation |
| Channick,[74] 1994 | Hypoxic canine model | 0-80 ppm | Hemodynamic values, $NO_2$, methemoglobin | Significant improvement in PVR with inhaled NO; no effect on $NO_2$ or methemoglobin production |
| Kavanagh,[77] 1994 | Isolated rabbit lung model of oxidant-induced acute lung injury | 90-120 ppm | Capillary permeability, pulmonary capillary pressure, and pulmonary vascular resistance | Inhaled NO protected against the development of increased capillary permeability in oxidant-induced acute lung injury |
| Jacob,[70] 1994 | Porcine model of hypoxic pulmonary vasoconstriction | 0-80 ppm | Hemodynamic & blood-gas values, methemoglobin, $NO_2^-$ & $NO_3^-$, nitrosylhemoglobin | Plasma levels of $NO_2^-$, $NO_3^-$ and methemoglobin increased with increasing [NO]. With 6-h NO administration, methemoglobin equilibrated at subtoxic levels, but $NO_2^-$ and $NO_3^-$ continued to rise. Nitrosylhemoglobin was not detected at any time |

protective against oxidant-induced lung injury. In an isolated-rabbit-lung model, Kavanagh et al[77] found that inhaled NO (90-120 ppm) protected against the development of increased capillary permeability in oxidant-induced acute lung injury. Using isolated rat lungs, Guidot et al[78] found that inhaled NO prevented neutrophil-mediated, $O_2$-radical dependent capillary leak and speculated that NO has anti-inflammatory properties.

### Human Studies

A number of reports on the use of inhaled NO in humans with ARDS have been published (Table 5[79-91]). The first papers describing the effects of inhaled NO with ARDS were by Rossaint et al[61] and Bigatello et al of our group.[73] Both showed an improvement in the ratio of arterial oxygen tension to fractional concentration of inspired oxygen ($P_{aO_2}/F_{IO_2}$) and PAP with no change in systemic hemodynamics when NO was administered by inhalation at ≤ 20 ppm (Fig. 8). Prolonged inhalation of NO did not result in tachyphylaxis. There was a rapid onset of effect with initiation of inhaled NO, and the effect was lost rapidly when NO was discontinued. Bigatello et al[73] found that patients with a mean PAP ≥ 30 mm Hg were more likely to respond to NO inhalation.

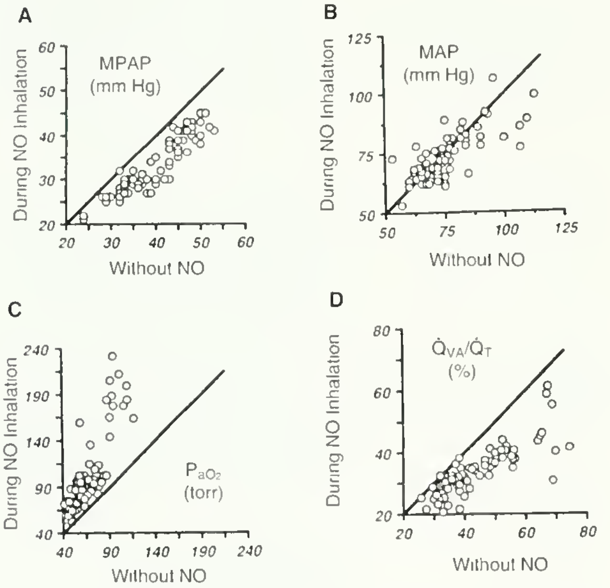

Fig 8. Individual responses of 7 patients with ARDS to inhaled NO during prolonged exposure. Values recorded daily without NO are plotted against values recorded during NO inhalation. The line crossing each panel represents identity between measurements obtained with and without NO inhalation (MPAP = mean pulmonary artery pressure, MAP = mean systemic arterial pressure, $P_{aO_2}$ = arterial oxygen tension, $\dot{Q}_{VA}/\dot{Q}_T$ = venous admixture). (Reprinted from Reference 73, with permission.)

Some patients with ARDS fail to respond to NO inhalation. In a retrospective analysis of their experience with inhaled NO, Rossaint et al[79] found that 17% of patients failed to increase their $P_{aO_2}/F_{IO_2}$ by at least 10 mm Hg and 37% of patients failed to decrease their mean PAP by at least 3 mm Hg. McIntyre et al[80] found a minimal improvement in $P_{aO_2}/F_{IO_2}$ and PAP in 5/16 trials (31%). Puybasset et al[82] found that 3 of 6 patients with ARDS and septic shock failed to respond to inhaled NO, and Wysocki et al[87] found that 10/17 (59%) failed to respond to inhaled NO. Although it has become clear that there are ARDS patients who do not respond to inhaled NO, the reasons for this are unclear, and at this time (1996) it is not possible to predict responders and nonresponders. The results of Bigatello et al[73] and Puybasset et al[90] suggest that the baseline level of PVR may affect response. Response may also be related to the degree of alveolar recruitment.[60,90] The issue of nonresponders is perplexing, and more laboratory and clinical investigation is necessary.

If inhaled NO improves $\dot{V}/\dot{Q}$, it might be expected that $V_D/V_T$ and $P_{aCO_2}$ as well as oxygenation would improve. Studies have shown small but significant improvements in $V_D/V_T$[80,82] and $P_{aCO_2}$.[85,89] We have also observed a small reduction in $V_D/V_T$ and $P_{aCO_2}$ in patients who respond to inhaled NO. However, this effect is too small to be clinically important and does not allow a reduction in minute ventilation.

The effects of NO inhalation on survival of patients with ARDS is unknown. All reports to date have been designed to evaluate the physiologic effects of inhaled NO—not survival. Evaluation of the effect of inhaled NO on survival requires a large double-blind placebo-controlled study, and several such studies are ongoing in the United States and Europe.

### Dose

The effective dose of inhaled NO is low. Initial studies showed improved oxygenation in patients with ARDS at doses ≤ 20 ppm.[61,73] Several groups have reported effective doses at < 5 ppm.[73,9,82,86,88,89] In patients with ARDS, Gerlach et al[86] found an $ED_{50}$ (defined by Gerlach et al as the dose that produced 50% of the desired effect) of 100 ppb for improvement of oxygenation and an $ED_{50}$ of 2-3 ppm for improvement of pulmonary artery pressure (Fig. 9). It is interesting to note that they found the beneficial effect peaked at about 10 ppm. It has been our practice to initiate inhaled NO therapy at a dose of 20 ppm. If oxygenation improves at that dose, then we decrease the inhaled NO to the lowest effective dose. At the doses commonly used with ARDS (≤ 20 ppm), inhaled NO is considered relatively free of toxicity. We have had no major complications related to inhaled NO in our patients (unpublished observation) and are aware of no reports of serious complications related to inhaled NO. However, there are several potential complications of this therapy that deserve consideration.

## Toxicity of Inhaled NO

### $NO_2$ Production

$NO_2$ is produced spontaneously from NO and $O_2$.[91-96] Although the Occupational Safety and Health Administration (OSHA) has set safety limits for $NO_2$ at 5 ppm,[1] airway reactivity[97] and parenchymal lung[98] injury have been reported with inhalation of as little as 2 ppm, and our clinical goal is to maintain inhaled $NO_2$ levels as low as possible.[99] We also

Table 5. Human Studies of Inhaled NO for ARDS. (See text for term definition)

| Reference & Year of Publication | Sample Size | NO Dose | Maximum Exposure | Outcome Variables | Major Findings |
|---|---|---|---|---|---|
| Rossaint[61] et al, 1993 | 10 | 0, 18, 36 ppm short-term; 5-20 ppm long-term | 53 days | Hemodynamic & blood-gas, multiple-inert-gas-elimination technique | Inhaled NO reduced PVR, increased arterial oxygenation, and improved $\dot{V}/\dot{Q}$; no systemic vasodilation |
| Bigatello[73] et al, 1994 | 13 | 0-40 ppm short-term; 2-20 ppm long-term | 27 days | Hemodynamic & blood-gas values | Inhaled NO reduced PVR & increased arterial oxygenation without systemic effects; effects greatest in patients with greatest degree of pulmonary hypertension |
| Rossaint[79] et al, 1995 | 87 | 0-25 ppm | 53 days | Retrospective review of clinical experience with inhaled NO; hemodynamic, blood-gas, & methemoglobin values | Improvement in oxygenation in ≅85% of patients & improvement in PAP in ≅65% of patients; no clinically significant change in methemoglobin; no evidence of tachyphylaxis |
| McIntyre[80] et al, 1995 | 14 | 0-40 ppm short-term; 2-20 ppm long-term | 10 days | Hemodynamic & blood-gas values | Minimal improvement in $P_{aO_2}/F_{IO_2}$ & PAP in 5/16 trials; concluded that although inhaled NO improves oxygenation and pulmonary hemodynamics in patients with ARDS, the effect is variable |
| Abman[81] et al, 1995 | 17 | 0-40 ppm short-term; 3-10 ppm long-term; pediatric patients | 24 days | Hemodynamic & blood-gas values | $P_{aO_2}/F_{IO_2}$ progressively increased at inhaled NO doses of 10 and 20 ppm, but no further increase at 40 ppm; decrease in PAP at 20 ppm, but no further decrease at 40 ppm |
| Puybasset[82] et al, 1994 | 11 | 0-2 ppm | — | Hemodynamic, blood-gas, end-tidal $P_{CO_2}$ values | Inhaled NO reversed the increase in PVR occurring with permissive hypercapnia; significant increase in arterial oxygenation during normocapnic & hypercapnic conditions; decrease in alveolar dead space with inhaled NO (n = 5) |
| Young[83] et al, 1994 | 14 | 0, 8, 32, 128 ppm | — | Hemodynamic & blood-gas values | Major beneficial effect of inhaled NO was improvement in oxygenation rather than reduction in PAP; degree of improvement in arterial oxygenation related directly to PVR before treatment |
| Levy[84] et al, 1995 | 20 | 0-10 ppm | 30 days | Hemodynamic & blood-gas values | Improvement in oxygenation in 19/20 patients, allowing reduction in $F_{IO_2}$ & PEEP; reduction in PAP with no change in systemic hemodynamics; 14/20 (70%) discharged |
| Fierobe[85] et al, 1995 | 13 | 0-5 ppm | — | Hemodynamic & blood-gas values | Inhaled NO reduced the afterload on the right ventricle without changing right ventricular output; hemodynamic effects of inhaled NO were not closely related to the improvement in arterial oxygenation |
| Gerlach[86] et al, 1993 | 12 | 0-100 ppm | — | Hemodynamic & blood-gas values | $ED_{50}$ for improvement of oxygenation was 100 ppb; peak effect for oxygenation was 10 ppm; $ED_{50}$ for reduction of PAP was 2-3 ppm |
| Wysocki[87] et al, 1993 | 17 | 0-10 ppm | — | Hemodynamic & blood-gas values | Effects of inhaled NO were small & not significant; 10/17 patients were nonresponders to inhaled NO; 7/17 patients had pronounced results with the combination of inhaled NO & almitrine |
| Gerlach[88] et al, 1993 | 3 | ≤ 1 ppb | 13 days | Hemodynamic & blood-gas values | Improvement in oxygenation occurred at <1 ppm; improvement in oxygenation with inhaled NO did not require reduction of PVR |
| Puybasset,[89] 1994 | 6 | 0-2 ppm | — | Hemodynamic & blood-gas values | Improvement in oxygenation & PVR with inhaled NO ≤ 2 ppm; small reduction in $P_{aCO_2}$ with inhaled NO |
| Puybasset[90] et al, 1995 | 21 | 2 ppm, with & without 10 cm $H_2O$ PEEP | — | Hemodynamic & blood-gas values | Factors affecting response of arterial oxygenation to inhaled NO were PEEP-induced alveolar recruitment & the baseline level of pulmonary hypertension |

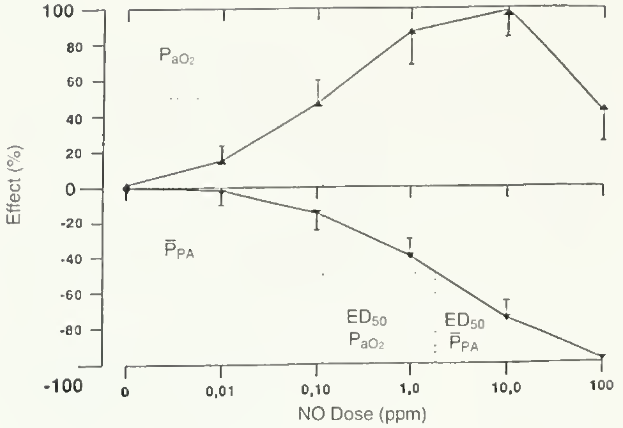

Fig. 9. Dose response for $P_{aO_2}$ and $\bar{P}_{PA}$ (mean pulmonary artery pressure) to inspiratory NO doses. Note that the estimated $ED_{50}$ of NO (defined by Gerlach et al as the dose that produced 50% of the maximal effect) for improvement of arterial oxygenation is ≈100 ppb (0.1 ppm); the estimated $ED_{50}$ for improvement of $\bar{P}_{PA}$ is ≈ 2-3 ppm. (Reprinted from Reference 86, with permission.)

keep the inhaled $NO_2$ as low as possible because its effects in an injured lung (eg, ARDS) are unknown. Because $NO_2$ is an atmospheric pollutant, its toxic pulmonary effects have been investigated in many studies as reviewed by Gong.[100] Animal studies evaluating the parenchymal effects of high levels of inhaled $NO_2$ (>10 ppm) have reported pulmonary edema, hemorrhage, changes in surface tension properties of surfactant, reduction in number of alveoli, and death.[101-104] Inhaled $NO_2$ at concentrations as low as 2 ppm produced alveolar cell hyperplasia, altered surfactant hysteresis, changes in the epithelium of the terminal bronchiole, and loss of cilia.[98,105] In humans, 2.3 ppm $NO_2$ was shown to affect alveolar permeability.[106] Several studies evaluating airway responses to low levels of inhaled $NO_2$ have reported conflicting results.[101] Some, however, have reported increased airway responsiveness at inhaled $NO_2 \leq 2$ ppm.[98,107,108] Inhaled $NO_2$ may remain in the lungs for prolonged periods of time because it reacts with water to produce nitric acid and undergoes irreversible absorption by the pulmonary epithelial lining fluid.[109] Exhaled $NO_2$, therefore, may not be a sensitive indicator of toxic pulmonary levels.

The extent of conversion of NO to $NO_2$ is determined by the residence time of NO with $O_2$ and is accelerated by increased NO concentrations and high $F_{IO_2}$.[91-96,99,110] The conversion rate of NO to $NO_2$ is determined by $O_2$ concentration, the square of NO concentration, and the residence time of NO with $O_2$. The kinetics of this is described by the relationship:[93,99]

$$\frac{-d[NO]}{dt} = k \cdot [O_2] \cdot [NO]^2 \qquad [1]$$

Because $O_2$ concentration is typically much greater than NO concentration, it is assumed that $O_2$ remains constant. It is also assumed that all of the conversion of NO is to $NO_2$. Integration of Equation 1 yields:

$$\frac{1}{[NO_t]} - \frac{1}{[NO_0]} = k \cdot [O_2] \cdot t \qquad [2]$$

where $[NO_t]$ is the NO concentration after a residence time $t$, $[NO_0]$ is the initial NO concentration, $[O_2]$ is the $O_2$ concentration, and $k$ is the rate constant for conversion of NO. The difference between $[NO_t]$ and $[NO_0]$ is the $[NO_2]$. Glasson and Tuesday[93] in 1963 reported the value of $k$ as $1.57 \times 10^{-9}$ $ppm^{-2}$ $min^{-1}$ at 23° C and a barometric pressure of 1 atmosphere. However, this rate constant was determined under static dry conditions and might differ in dynamic systems such as adult mechanical ventilation. We found a rate constant of $1.46 \times 10^{-9}$ $ppm^{-2}$ $min^{-1}$ when NO was blended with $N_2$ before entering the ventilator and observed that it increased 8-fold to $1.17 \times 10^{-8}$ $ppm^{-2}$ $min^{-1}$ when NO was blended with air before introduction into the ventilator (Fig. 10).[99] Adia et al[110] found that the rate constant was smaller at 37° C than 25° C, but that it was not affected by humidity.

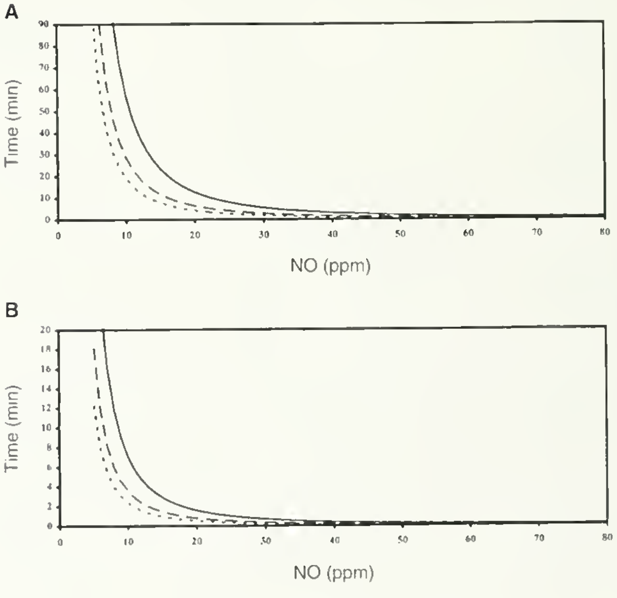

Fig. 10. Time required to generate 2 ppm $NO_2$ in a mechanical ventilator system using rate constants published by Nishimura et al.[99] A. NO (800 ppm) mixed with nitrogen before introduction into the ventilator. B. NO (800 ppm) mixed with room air before introduction into the ventilator system. Note that the generation of $NO_2$ is accelerated when NO is mixed with air due to the presence of oxygen in air (———— = 30% oxygen, ------- = 60% oxygen, and = 90% oxygen).

In breathing systems, $NO_2$ concentration is greater with increased NO concentration, higher $F_{IO_2}$, or lower $\dot{V}_E$.[94-96] The $NO_2$ concentration delivered to the patient is also greater for ventilators with a higher internal volume (eg, Servo 900C) than for those with a lower internal volume (eg, Puritan-Bennett 7200ae) because this increases the residence time of NO with $O_2$.[99]

There is a potential for NO conversion to $NO_2$ in lung units with long residence times. We have observed that levels of exhaled nitric oxide of 50-75% of inhaled levels are common when inhaled NO is administered to patients with ARDS. Data from our laboratory indicate that a relatively long residence time is required to produce 2 ppm $NO_2$ at the NO concentration typically used in the treatment of ARDS (ie, $\leq 20$ ppm).[99] At a rate constant of $1.46 \times 10^{-9}$ $ppm^{-2} min^{-1}$, the time required to produce 2 ppm $NO_2$ is 4.6 min when the breathing mixture is 90% $O_2$ and 6.8 min when it is 60% $O_2$. Such prolonged residence times are unlikely during ARDS but might occur in patients with severe chronic airflow obstruction. Further work is needed to determine whether conversion of NO to $NO_2$ does occur in the lungs during NO administration.

A soda lime absorber in the inspiratory circuit can be used to remove $NO_2$.[91,110-112] Stenqvist et al[111] evaluated the effectiveness of soda lime to absorb $NO_2$ and reported that 3 ppm $NO_2$ decreased to less than 1 ppm after passing through the absorber. However, soda lime also absorbs NO,[111] its effectiveness decreases over time, and some forms of soda lime may be ineffective in removal of $NO_2$.[112] The use of a soda lime canister introduces other potential problems during mechanical ventilation such as increased resistance to breathing, increased risk of system leaks, increased compression volume, more difficult triggering of the ventilator, and modification of inspiratory flow waveforms.

### Methemoglobinemia

Methemoglobin is produced when the iron in heme is oxidized from $Fe^{++}$ to $Fe^{+++}$.[113] Unlike any other gas, NO binds to $Fe^{++}$ and $Fe^{+++}$. In the oxidized form, iron cannot bind to $O_2$ and the affinity of the other heme groups for $O_2$ increases (ie, shifts the oxyhemoglobin dissociation curve to the left). Normal methemoglobin is < 2% and levels < 5% do not require treatment. Normal metHb levels may be due, in part, to metabolism of endogenous NO. A number of oxidizing agents can produce methemoglobinemia. A common cause of methemoglobinemia is exposure to nitrates. Methemoglobin reductase within the erythrocyte converts endogenously produced methemoglobin to normal hemoglobin. NADH-methemoglobin reductase is predominant and reduces two thirds of the metHb produced.

The light absorption of methemoglobin differs from that of normal hemoglobin. This allows measurement of methemoglobin levels by multiple wavelength spectrophotometry (CO-oximetry).[114] Because pulse oximetry uses only two wavelengths and cannot distinguish between oxyhemoglobin and methemoglobin, its accuracy is affected by the presence of methemoglobin.[115] Infusion of the reducing agent methylene blue for treatment of methemoglobinemia may also affect the accuracy of pulse oximetry.[115] This is due to the effects of circulating methylene blue on light absorption at the wavelengths used by pulse oximeters.

Production of methemoglobin by NO exposure has been known for years,[67-69,116-120] and the high affinity of hemoglobin for NO explains the selectivity for inhaled NO on the pulmonary vasculature (described earlier). It has been recognized for many years that high inhaled NO concentrations ($\geq 2\%$) rapidly produce methemoglobinemia and death in dogs.[67] However, other animal studies have shown that methemoglobinemia does not constitute a problem at the doses commonly used with ARDS (< 20 ppm).[61,73,79] Azoulay et al[121] exposed rats to 2 ppm inhaled NO continuously for 6 weeks and methemoglobinemia did not occur. Similar results have been reported in humans (Fig. 11).[61,73,79-81,83] It is our practice to monitor methemoglobin levels daily for patients receiving inhaled NO. If a rare upward trend in the methemoglobin level occurs, this can usually be controlled by using a lower but still effective NO dose. In our experience with inhaled NO in more than 100 patients, we have had only one case in which the methemoglobin exceeded 5%.[122]

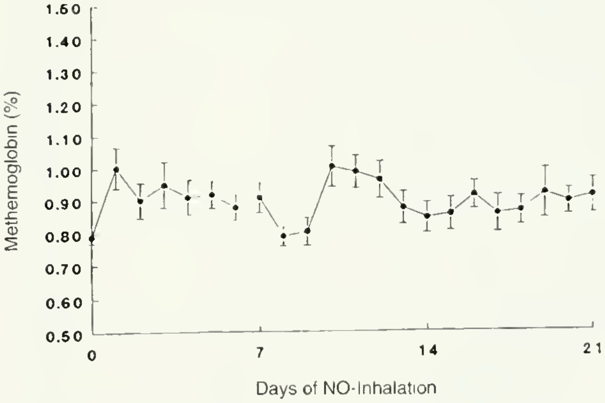

Fig. 11. Methemoglobin levels during the first 3 weeks of NO inhalation in 30 patients inhaling an average of ≈10 ppm for an average of ≈17 days. (Reprinted from Reference 79, with permission.)

The usual treatment of methemoglobinemia is infusion of methylene blue, which increases NADH-methemoglobin reductase. Methemoglobinemia can also be treated with ascorbic acid (vitamin C). Because methylene blue may inhibit the effect of guanylate cyclase, there is concern that its use might counteract the effects of inhaled NO. This was studied by Young et al[123] in hypoxic sheep, and they found that methylene blue did not inhibit the action of inhaled NO on guanylate cyclase.

### Production of Peroxynitrite

Little is known about the potential intracellular toxicity of inhaled NO at the doses used with ARDS. Superoxide ($O_2^-$)

reacts with NO to produce peroxynitrite ($ONOO^-$),[124,125] a strong oxidant that readily catalyzes membrane lipid peroxidation. However, it is possible that inhaled NO may also scavenge $O_2^-$ by this pathway and decrease oxidant-induced lung injury. Whether peroxynitite production is helpful or harmful to patients with acute lung injury is unknown.

## Adverse Effects of Inhaled NO

### Platelet Inhibition

Inhibition of platelet aggregation by NO was demonstrated by Mellion et al[126] and Radomski et al.[127,128] In vitro studies have shown that NO causes antiplatelet effects by activating guanylate cyclase and, thus, increasing platelet cGMP.[129-132] This results in inhibition of platelet adhesion, aggregation, and agglutination. When rabbits were exposed to 30 and 300 ppm of inhaled NO, bleeding time increased at 15 min by 46% with 30 ppm and 72% with 300 ppm.[133] When healthy volunteers were exposed to 30 ppm inhaled NO for 15 min, bleeding time increased by 33% (Fig. 12).[134]

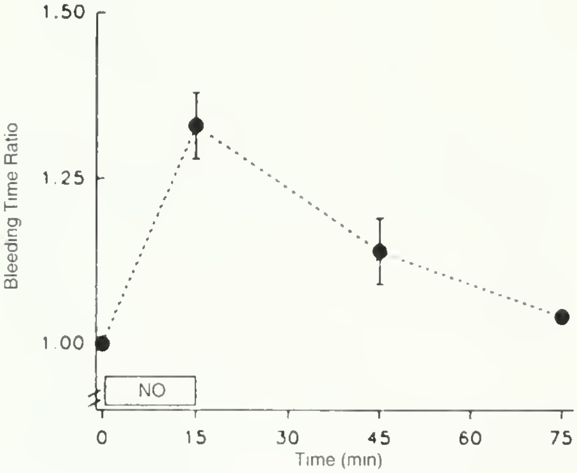

Fig. 12. Bleeding time ratios (ie, bleeding time after administration/bleeding time before) for 6 healthy volunteers after breathing 30 ppm NO for 15 min. (Reprinted from Reference 132, with permission.)

The effect of inhaled NO on platelet aggregation in patients with ARDS was examined by Samama et al.[134] Platelet function and bleeding time were examined in 6 patients with inhaled NO levels randomly administered at 1, 3, 10, 30, and 100 ppm. Platelet aggregation and agglutination were significantly decreased at each NO dose. The NO-induced inhibition of platelet function was not dose-dependent, and the maximal inhibition occurred at 3 ppm. However, the antithrombotic effect was not associated with a change in bleeding time (Fig. 13). Although it is prudent to consider coagulopathy when deciding to use inhaled NO for an ARDS patient, this effect may not be clinically important.

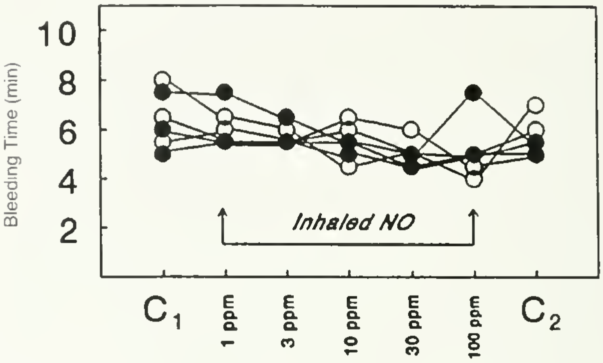

Fig. 13. Changes in bleeding time induced by administration of 5 randomly selected concentrations of inhaled NO (1, 3, 10, 30, 100 ppm) to 6 patients with ARDS. Note that inhaled NO did not affect bleeding times. (Reprinted from Reference 134, with permission.)

### Increased Left Ventricular Filling Pressure

Several studies have examined the effects of inhaled NO in patients with left ventricular dysfunction.[135-137] At high doses (40-80 ppm), inhaled NO has been shown to decrease PVR and elevate pulmonary capillary wedge pressure in such patients (Fig. 14). One presumes that the reduction in right ventricular afterload causes an increase in right ventricular output. The resultant acute increase in left ventricular filling could produce pulmonary edema in patients with pre-existing left ventricular dysfunction. Although this effect may be less with the doses commonly used for ARDS (≤ 20 ppm), we generally avoid the use of inhaled NO in patients with documented left ventricular failure.

### Rebound Hypoxemia & Pulmonary Hypertension

Gerlach et al[88] and then Bigatello et al[73] reported that withdrawal of inhaled NO could present a problem in some patients. Roissant et al[61] reported a decrease in arterial oxygenation and an increase in PAP with daily trials of NO withdrawal (Fig. 15). Miller et al[138] reported rebound pulmonary hypertension with withdrawal of inhaled NO (Fig. 16). It has been our clinical experience that rebound commonly occurs when inhaled NO is discontinued. To be specific, a transient (4-8 h) deterioration in oxygenation occurs, and pulmonary hypertension develops, which may be potentially life-threatening in some patients. The reasons for this rebound effect are not entirely known but may relate to feedback inhibition of NO-synthase activity.[139,140]

We follow several guidelines to avoid the deleterious effects of rebound during withdrawal of inhaled NO. First, we decrease the NO to the lowest effective dose (≤ 5 ppm).

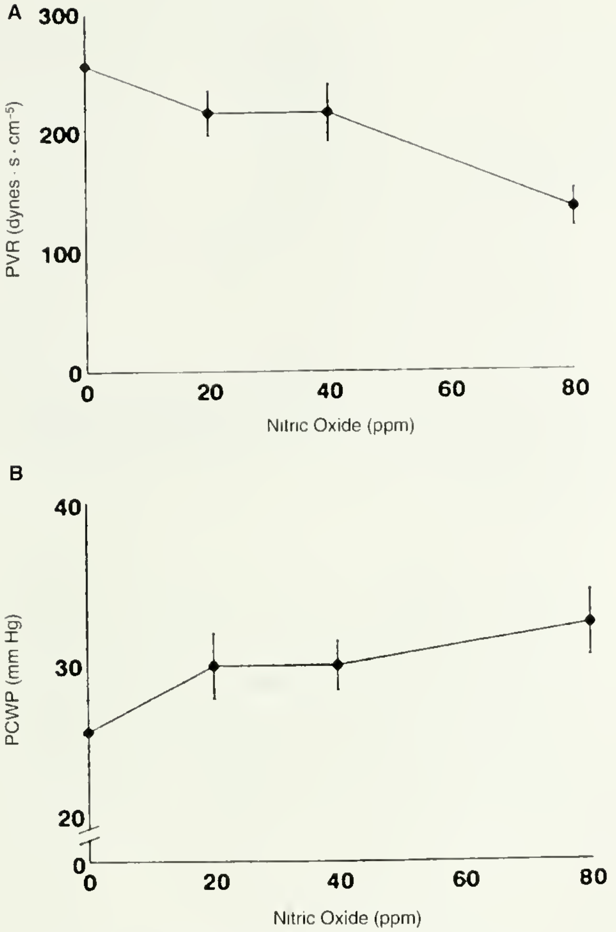

Fig. 14. A. Relationship between dose of inhaled NO and pulmonary vascular resistance (PVR). B. Relationship between dose of inhaled NO and pulmonary capillary wedge pressure (PCWP). Note that the reduction in PVR is associated with an increase in PCWP. (Reprinted from Reference 137, with permission.)

Second, we do not withdraw inhaled NO until the patient's clinical status has improved sufficiently (eg, $F_{IO_2} = 0.40$, PEEP = 5 cm $H_2O$, hemodynamically stable). Third, we increase the $F_{IO_2}$ to 0.60-0.70 before withdrawal of inhaled NO and prepare to support the patient's hemodynamics if necessary. We have found that increasing the $F_{IO_2}$ from 0.40 to 0.70 is sufficient to prevent the clinical sequelae of inhaled NO withdrawal.

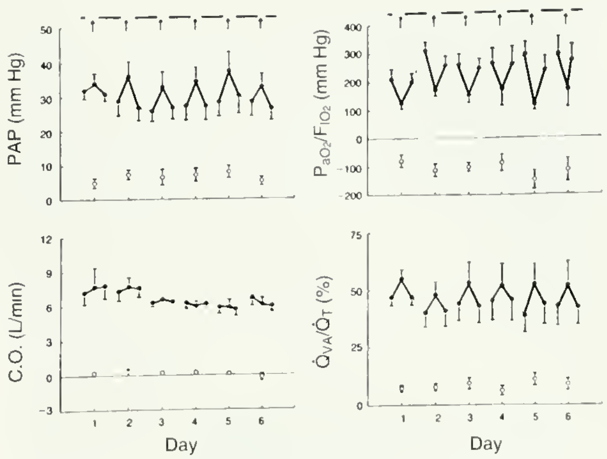

Fig. 15. Hemodynamic function and gas exchange before, during, and after brief interruptions (arrows) of inhaled NO (bars) during the first 6 days of treatment in 7 patients with ARDS. Note the large changes in pulmonary artery pressure (PAP), arterial oxygen tension ($P_{aO_2}$), ratio of arterial oxygen tension to fractional concentration of inhaled oxygen ($P_{aO_2}/F_{IO_2}$), and ratio of pulmonary to total shunt ($\dot{Q}_{VA}/\dot{Q}_T$) when NO was acutely discontinued. For this reason, we do not recommend on/off trials to assess NO responsiveness. (Reprinted from Reference 61, with permission.)

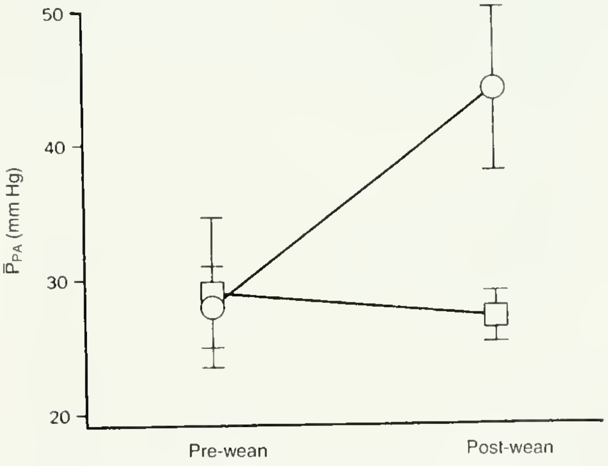

Fig. 16. Rebound pulmonary hypertension during withdrawal of inhaled NO (○) or placebo (□). Pre-wean represents mean pulmonary artery pressure ($\bar{P}_{PA}$) before attempting weaning; post-wean represents highest $\bar{P}_{PA}$ during weaning of study gas. (Reprinted from Reference 138, with permission.)

## NO Delivery Systems

No commercial systems for delivery of inhaled NO are now available, and the devices used vary considerably from institution to institution. We believe that the following are important considerations when building a system for delivery of inhaled NO:[141]

- Dependable and safe system: Inhaled NO is used with the most critically ill patients, and complex systems are vulnerable to errors that could compromise ventilation, oxygenation, or delivery of the correct NO concentration. The function of NO delivery systems must be thoroughly evaluated in the laboratory before patient use, and these evaluations should be published to assist others.

- Precise and stable NO dose delivery: It is important to deliver a precise and stable dose to avoid complications associated with inhaled NO. NO is typically supplied from a cylinder with a high NO concentration (800-2200 ppm of NO in $N_2$). It is then diluted with $N_2$, air, or $O_2$ before delivery to the patient. The choice of cylinder concentration is determined by safety and convenience. A higher concentration is convenient (fewer cylinder changes and/or smaller cylinders) but increases the risk of exposure to high NO and $NO_2$ (for both the patient and bedside care providers). A source gas with a higher NO concentration also allows delivery of a higher $F_{IO_2}$ due to less dilution (ie, lower flow) from the NO source.

- Limit $NO_2$ production: Our clinical goal is to maintain inhaled $NO_2$ as low as possible (always < 2 ppm). At NO doses ≤ 20 ppm, the risk of significant $NO_2$ production in adult ventilator systems is low unless the $F_{IO_2}$ is high (≥ 0.9) and the minute ventilation is low (≤ 5 L/min). Although the use of soda lime has been recommended to limit $NO_2$ delivery, significant $NO_2$ generation can be minimized by proper system design.

- NO and $NO_2$ monitoring: Many clinical centers that are administering inhaled NO have developed nomograms to assist with proper dosing. However, there is imprecision of the blenders used to mix NO, $N_2$, and $O_2$—none of which have been calibrated for use with NO. Therefore, it is important to directly monitor inhaled NO and also to monitor inhaled $NO_2$ because of its potentially injurious effects.

- Permit scavenging of NO: Legitimate concerns exist regarding contamination of the environment with NO and $NO_2$ and the potential for adverse effects on health care providers at the bedside. OSHA has set exposure limits for NO at a time-weighted average of 25 ppm for 8 hours in the workplace. This is higher than the typical NO dose (≤ 20 ppm). In intensive care environments that have > 6 air exchanges/h, ambient NO levels should remain very low. It has been our experience that ambient NO levels are low during NO administration (< 0.25 ppm) with or without scavenging (Fig. 17). Nonetheless, we do scavenge the exhaled gases during NO therapy. It is important that the scavenging system be constructed so that it does not affect the function of the ventilator and does not increase the expiratory resistance. It should be appreciated that scavenging gases from the exhalation port of the ventilator does not completely eliminate ambient contamination because the ventilator may internally leak gas (containing NO) as part of its normal operation.

- Maintain proper ventilator function: Care must be taken to assure that adapting the ventilator to deliver NO does not affect ventilator function. In particular, the alarm systems should not be affected. The addition of NO lowers the $F_{IO_2}$, and for that reason $O_2$ concentration should be monitored distal to the site of NO titration into the system. (Note that it is impossible to deliver 100% $O_2$ during inhaled NO therapy.) There is concern regarding the effect of NO on the internal components of the ventilator and the external blenders and flowmeters exposed to NO. However, we have not detected damage or malfunction of equipment related to NO exposure, even after thousands of hours of exposure (unpublished observation).

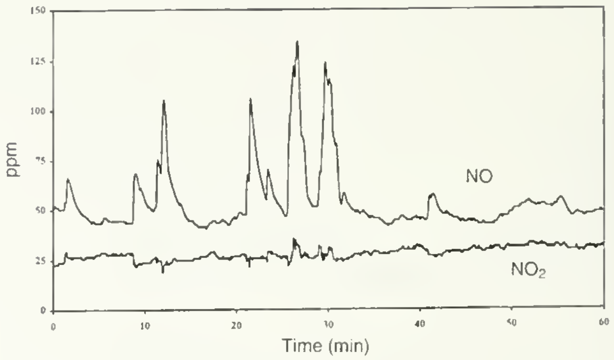

Fig. 17. Ambient NO and $NO_2$ levels for 1 hour with 100 ppm NO delivered into an ICU room at 8 L/min. NO and $NO_2$ measured by chemiluminescence 10 ft from NO flow. Note that ambient NO and $NO_2$ levels remain low with no scavenging other than usual room ventilation.

## Techniques for NO Delivery

### Adult Mechanical Ventilators

A simple method for delivering NO is continuous administration into the inspiratory limb of the ventilator circuit.[83,142] The mean NO concentration delivered to the patient is estimated from the NO flow and the inspiratory flow. We do not recommend such systems for use with adult ventilators that have phasic flow (ie, flow only during inspiration). With such systems, the inspiratory circuit fills with NO during expiration and a large bolus of NO is delivered to the patient with the beginning of each breath. NO delivery is also affected by changes in the inspiratory flow waveform, the minute ventilation, the site at which NO is titrated into the circuit, and the ratio of inspiratory-to-expiratory time (I:E). The additional flow augments tidal volume (with either pressure or volume ventilation), and triggering is not possible unless the patient's inspiratory flow exceeds the NO flow.

If NO is continuously added at the Y-piece,[84,87,134,143] the inspiratory circuit does not fill with NO during expiration. Instead, the NO bleeds out the expiratory limb of the ventilator during expiration. Most important, however, it is not possible to measure the inspired NO concentration with this method, and the dose can only be approximated by mathematical calculation. This system suffers many of the same limitations of NO titration into the inspiratory circuit—specifically, augmentation of tidal volume, decreased ability to trigger the ventilator, and changes in delivered concentration of NO with changes in inspiratory flow.

A constant flow of NO has also been delivered through the endotracheal tube into the trachea.[85] Problems associated with this method are similar to titration at the Y-piece. In addition, we believe that this method can be dangerous. During accidental disconnection, $O_2$-free NO gas continues to flow into the trachea and quickly produces hypoxia.

NO may be injected into the ventilator circuit during the inspiratory phase.[61,81,82,89,90] This has been accomplished by using a nebulizer-drive mechanism that operates during inspiration. The gas supply to the nebulizer contains the NO required to achieve the desired patient dose after being mixed with gas delivered from the ventilator. Because the gas flow from the nebulizer is constant during inspiration, this method delivers a constant NO dose only with constant flow ventilation. It does not work well with varying inspiratory flow patterns such as pressure control. Also, this method does not deliver a stable dose with ventilatory modes such as pressure support in which tidal volume and inspiratory time vary from breath to breath. The major benefit of this method is that it minimizes $NO_2$ generation because the residence of NO in an $O_2$-containing gas mixture is minimized. However, this method does not allow precise control of the inspired NO concentration and is available with only a few ventilator systems. For this method to be acceptable, flow from the ventilator must be continuously and precisely measured, and the injected dose of NO must be precisely titrated so that the delivered NO and inspiratory flow waveform are not affected.

Several papers describe systems to administer inhaled NO to adult mechanically ventilated patients by premixing the NO with $N_2$ (or air) and introducing the mixture proximal to the gas inlet of the ventilator.[73,74,80,99,111,143-145] These systems typically add the $O_2$-$N_2$-NO gas mixture to the low-flow inlet of the Servo 900C ventilator or the high-pressure air or $O_2$ inlet of a ventilator such as the Puritan-Bennett 7200.

At the Massachusetts General Hospital, we have designed a system to accomplish this using the Puritan-Bennett 7200 ventilator (Fig. 18).[99] An air-$O_2$ blender is used to add NO (eg, 800 ppm) to the $O_2$ inlet of the blender, and $N_2$ or air is added to the air inlet of the blender. The choice of air or $N_2$ as the diluent is determined by the extent of $NO_2$ generation. NO must be mixed with $N_2$ with high NO doses (> 20 ppm), high $F_{IO_2}$ (eg, > 0.90), or low minute ventilation (< 5 L/min). The gas mixture leaving the blender is delivered to the high-pressure air inlet of the ventilator. The final NO concentration delivered to the patient is determined by the $F_{IO_2}$ settings on the external blender and the ventilator. Although we have developed nomograms to assist the respiratory therapist at the bedside in determining the correct blender setting to achieve the desired NO concentration (see Nomogram), we always confirm the delivered NO concentration by direct measurement. It is also important to analyze $F_{IO_2}$ due to the effect of $NO/N_2$ dilution on delivered $F_{IO_2}$. It has been our experience and that of others that air-$O_2$ blenders do not always deliver a precise NO concentration (Fig. 19).[146] This becomes likely when flow from one of two or more blenders in series is less than that required for accurate gas mixing. Although multiple blenders in series can be used to reduce the NO concentration, we have found such systems to be superfluous and unnecessarily complex.

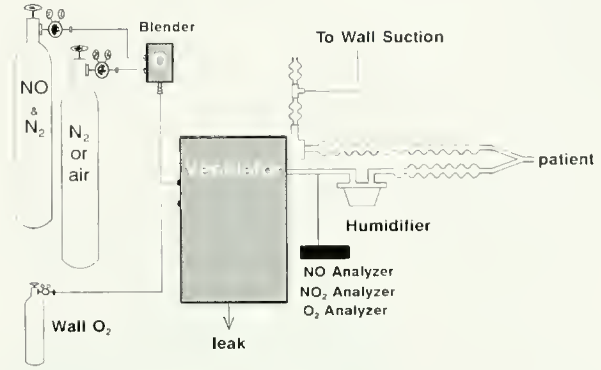

Fig. 18. NO delivery system used for mechanically ventilated patients at the Massachusetts General Hospital. NO (800 ppm) is mixed with $N_2$ (or air) and introduced into the air inlet of the ventilator (Puritan-Bennett 7200). The external blender setting and ventilator $F_{IO_2}$ setting determine the delivered NO concentration. NO, $NO_2$, and $O_2$ are measured at the ventilator outlet. Exhaled gas leaving the ventilator is scavenged to wall suction. Note that leakage of gas form the ventilator into the room may affect ambient NO concentration.

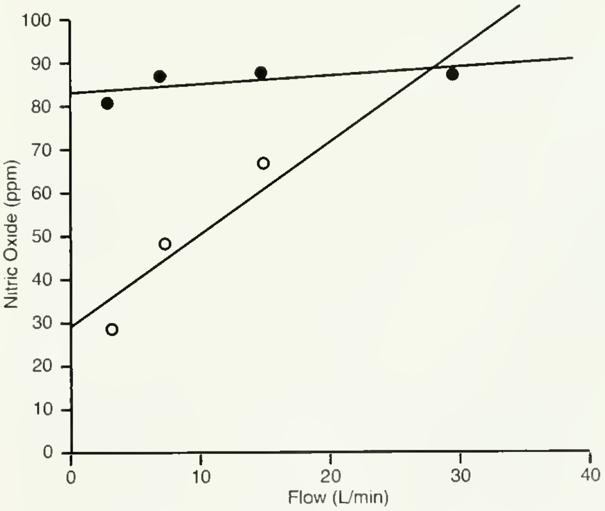

Fig. 19. Nitric oxide concentration of output gas from three different double-blender systems (ie, two blenders in series to dilute the source NO concentration). Two systems (grouped together, ○) demonstrated a linear increase in NO concentration with increasing gas flow. The third system (●) demonstrated a stable NO concentration with changes in flow. The 3 blender pairs were set to deliver the same NO concentration (83 ppm). (Adapted from Reference 146, with permission.)

**Nomogram***

External Blender Settings and Ventilator $F_{IO_2}$ Settings To Achieve Approximate Delivered NO Concentrations

1. The $N_2$-NO mixture (NO 800 ppm) is added to $O_2$ inlet of external blender.
2. $N_2$ or air is added to air inlet of blender.
3. Outlet of external blender leads to air inlet of ventilator.
4. Actual delivered dose must always be confirmed by analysis.

*This nomogram has been used successfully at the Massachusetts General Hospital since 1993 in conjunction with a Puritan-Bennett 7200 ventilator and a Bird blender.

| Ventilator $F_{IO_2}$ Setting | External Blender Setting | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 100 | 90 | 80 | 70 | 60 | 50 | 40 | 30 | 29 | 28 | 27 | 26 | 25 | 24 | 23 | 22 |
| | Approximate Delivered NO Concentration (ppm) | | | | | | | | | | | | | | | |
| 0.90 | 101 | 88 | 76 | 63 | 50 | 37 | 24 | 12 | 10 | 9 | 8 | 6 | 5 | 4 | 3 | 1 |
| 0.80 | | | | | 100 | 74 | 49 | 23 | 21 | 18 | 15 | 13 | 10 | 8 | 5 | 3 |
| 0.70 | | | | | | | 73 | 35 | 31 | 27 | 23 | 19 | 15 | 12 | 8 | 4 |
| 0.60 | | | | | | | 97 | 46 | 41 | 36 | 31 | 26 | 21 | 15 | 10 | 5 |
| 0.50 | | | | | | | | 58 | 51 | 45 | 38 | 32 | 26 | 19 | 13 | 6 |
| 0.40 | | | | | | | | 69 | 62 | 54 | 46 | 38 | 31 | 23 | 15 | 8 |
| 0.30 | | | | | | | | 81 | 72 | 63 | 54 | 45 | 36 | 27 | 18 | 9 |
| 0.21 | | | | | | | | 91 | 81 | 71 | 61 | 51 | 41 | 30 | 20 | 10 |

Premixing before introduction into the ventilator has the advantage that the NO dose is constant throughout inspiration and is not affected by changes in minute ventilation or flow waveform, but, as we stated earlier, $NO_2$ production is greater with ventilators that have large internal volumes.[99] One potential disadvantage of this system is that the NO dose changes when the ventilator $F_{IO_2}$ setting is changed. However, it is easy to compensate for this by adjusting the setting on the external blender. Another issue with this system relates to the function of the nebulizer system of the ventilator. With some ventilators (eg, Puritan-Bennett 7200), the gas used to power the nebulizer is either air or $O_2$, depending on the $F_{IO_2}$. Because NO is added via the air inlet of the ventilator, activation of the nebulizer for bronchodilator delivery may affect the delivered NO concentration. This potential problem can be avoided by use of an inhaler instead of a nebulizer.

Current-generation ventilators use microprocessor technology to set the delivered oxygen concentration. It seems reasonable to use similar technology to set the delivery of other gases such as NO. Microprocessor technology coupled with precision solenoids could be used to mix air, $O_2$, and NO to achieve the desired $F_{IO_2}$ and NO concentration. Such systems are available in Europe.[88] However, it is unlikely that industry will release these systems in the United States until inhaled NO is approved by the FDA for general clinical application.

### Pediatric Mechanical Ventilators

For continuous-flow ventilators, such as those used in pediatrics (including high frequency oscillators), NO can be titrated into the inspiratory limb of the ventilator circuit.[147-150] The ideal is titration into the system near the ventilator outlet, for adequate mixing before reaching the patient; and oxygen concentrations should be analyzed distal to the point of NO introduction into the system. $NO_2$ generation should be relatively low because the residence time in the system is short. The expected NO can be calculated as:

$$[NO] = \frac{(\text{NO flow})\,(\text{source ppm})}{(\text{NO flow} + \text{ventilator flow})}. \qquad [3]$$

However, this should be considered an approximation, and the actual delivered NO concentration should be measured. Once the NO concentration has been established, the dose remains constant provided that the total flow through the system does not change. Systems using this approach have been evaluated by others[147] and by us[150] and have been found to be reliable.

### Manual Ventilators

For manual ventilation, NO can be diluted with $O_2$ and introduced into the gas inlet port of the manual ventilator.[147,151] We have used this system with self-inflating resuscitators as well as gas-inflating resuscitators. The expected NO concentration can be calculated as:

$$[NO] = \frac{(\text{NO flow})\ (\text{source ppm})}{(\text{NO flow} + O_2\ \text{flow})}. \qquad [4]$$

Before using this system to ventilate the patient, the delivered NO concentration ideally should be analyzed to assure the correct delivered dose. It must be recognized that NO delivery may change with changes in minute ventilation if the flow into the manual ventilator is less than the minute ventilation. We have used this system for bedside manual ventilation and during patient transport for diagnostic procedures. Because this system is used only intermittently, care must be taken to avoid $NO_2$ generation between uses. This could potentially result in a large $NO_2$ delivery if the resuscitator is not used for a prolonged time. This is easy to avoid by adequately flushing the resuscitator with $O_2$ before and after each use. Although some have described the use of a potassium permanganate air-filtration medium to scavenge exhaled NO and $NO_2$ during the use of manual ventilators,[147] we have generally not found this to be necessary—particularly with the low doses ($\leq 20$ ppm) that we typically use with ARDS.

### Spontaneous Breathing

Although ARDS patients requiring inhaled NO are usually mechanically ventilated, inhaled NO can be delivered to spontaneously breathing patients, and several systems have been described. A high-flow system with a tight-fitting face mask can be used,[145] and the expected NO concentration can be calculated by Equation 3.

Exhaled gas can be scavenged by the hospital vacuum system. Reservoir bags should be avoided with these systems because of the likelihood of $NO_2$ generation within the bag.

Inhaled NO can also be administered to spontaneously breathing patients using a transtracheal $O_2$ catheter[152] or a nasal cannula,[153] but there are several limitations to these systems. It is not possible to analyze the delivered dose, the dose varies with the ventilatory pattern of the patient (Fig. 20), and it is also difficult to scavenge NO.

## NO & $NO_2$ Analysis

Regardless of the method used to deliver NO, it is mandatory to monitor the delivered dose. Due to its toxicity, it is also desirable to monitor $NO_2$. The principal methods used to monitor NO and $NO_2$ are chemiluminescence and electrochemical analysis.

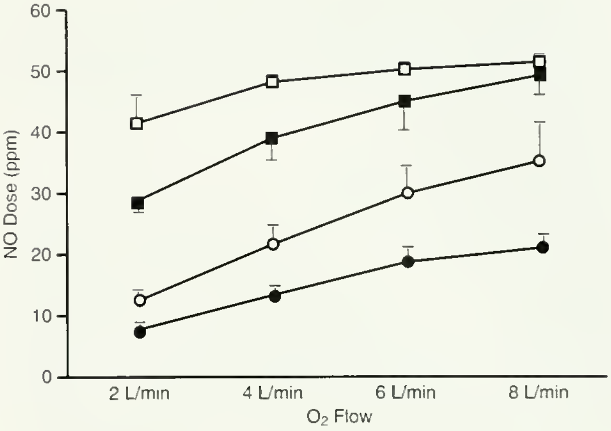

Fig. 20. NO inhaled by nasal cannula; 100 ppm NO delivered to the cannula. NO varies with changes in tidal volume (ie, ● = 1.5 L, ○ = 1.0 L, ■ = 0.5 L, and □ = 0.25 L) and cannula flow. Data collected using a lung model of spontaneous breathing. Data from Reference 153.

### Chemiluminescence Analyzers

The established method for NO and $NO_2$ analysis is chemiluminescence,[154-156] a method that has been used for many years in industrial and environmental applications and can be adapted to biomedical uses. In this method, sample gas reacts with ozone ($O_3$) to produce activated $NO_2$, or $NO_2^*$:

$$NO + O_3 \rightarrow NO_2^* + O_2. \qquad [5A]$$

$NO_2^*$ changes back to ground state by emitting electromagnetic radiation:

$$NO_2^* \rightarrow NO_2 + h\nu. \qquad [5B]$$

The maximum radiation is emitted at 1200 nm and is detected photoelectrically. To be measurable, $NO_2$ must first be converted to NO in a thermal converter (325° C) containing molybdenum (Mo):

$$3\ NO_2 + Mo \rightarrow 3\ NO + MoO_3. \qquad [5C]$$

The sum of NO measured with and without the converter is referred to as NOx ([NOx] = [NO] + [$NO_2$]). Most chemiluminescence analyzers measure NO and NOx simultaneously and display [NO], [NOx] and [$NO_2$]. A potential problem with chemiluminescence is quenching.[157-160] Some of the $NO_2^*$ produced by ozonation of NO changes to ground state by reacting with other molecules (eg, $O_2$, $N_2$, $H_2O$, $CO_2$). The greater the concentrations of these quenching molecules, the lower is the chemiluminescence, and the NO and NOx values will be in error. The effects of quenching can be mathematically corrected or avoided by calibrating the analyzer with the same gases present that will be present during analysis. The quenching effect is also less with a molybdenum than with a stainless steel conversion chamber, and with thorough removal of $H_2O$ from the sample.

### Electrochemical Analyzers

Chemiluminescence analyzers are accurate and precise. However, they are also typically large, expensive, and cumbersome to use. Electrochemical cells have recently become available to measure both NO and $NO_2$. These are designed specifically for medical applications and are small, portable, rugged, and less expensive than chemiluminescence devices. Electrochemical analyzers generate a potential difference proportional to the concentrations of NO and $NO_2$, from reactions of NO and $NO_2$ within an electrolyte. Evaluations of these devices have found them to be suitably accurate for clinical use.[161-169] Because electrochemical NO cells are affected by humidity, they should sample NO before the gas is humidified. These cells are also pressure sensitive, but this effect can be lessened by use of sidestream sampling techniques.

### Inspired, Tracheal, & Expired Gas Analysis

Most chemiluminescence and electrochemical analyzers have slow response times.[170] Thus, the displayed concentrations of NO and $NO_2$ are time-weighted averages. This is important to appreciate because real-time fluctuations in NO delivery are not detected by these methods. This can result in a deceptive impression of the characteristics of the NO delivery pattern and dose.

Most commonly, NO concentration is measured in the inspiratory limb of the ventilator circuit. This location accurately reflects the NO concentration delivered to the lungs. NO concentration has also been measured in tracheal gas;[82,89,90,134] however, tracheal NO concentration is affected by changes in expiratory NO concentrations and by the ventilatory pattern (Fig. 21).[171] Inhaled concentrations of NO should be measured and reported in a reproducible manner. To compare the results of clinical studies, we believe that NO concentration should be analyzed from the inspiratory limb of the ventilator circuit.

### In Summary

Although it is likely to be several years before NO is approved for general clinical use, all clinicians caring for critically ill patients should become familiar with this therapy. Because it is administered by inhalation, delivery systems for NO legitimately fall within the practice of respiratory therapists. Regardless of the future role of inhaled NO as a therapeutic agent, its investigational use is teaching us much about inhaled selective pulmonary vasodilators and the development of safe delivery systems for such agents.

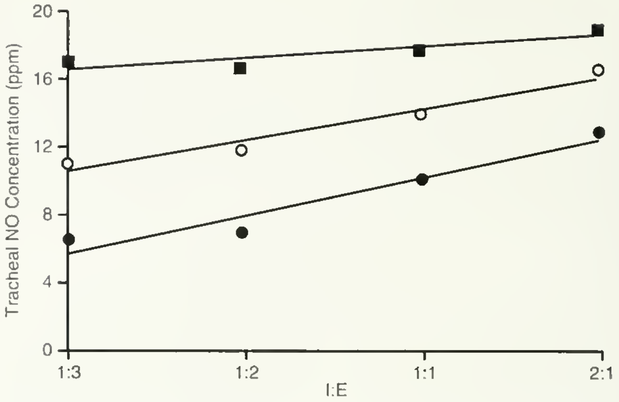

Fig. 21. Tracheal NO concentration at 4 I:E and 3 expired-NO concentrations (● = 0 ppm, ○ = 7 ppm, and ■ = 14 ppm). Data collected using a lung model with inspired NO concentration of 20 ppm. Note that tracheal NO concentration varies with changes in expired NO concentration and I:E. For this reason, we recommend that the NO dose always be measured from the inspiratory limb of the ventilator circuit. Data from Reference 171.

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## Hess Discussion

**Slutsky**: In terms of responders and nonresponders, you showed that the patients with increased mean pulmonary artery pressures are more likely to respond. Jean Jacques Rouby and his group[1] showed the critical variable in their study to be pulmonary vascular resistance (PVR), which makes a lot of sense. If you have a high pulmonary artery pressure due to increased cardiac output, there's no reason you'd expect nitric oxide to work. Do you find the same thing?

**Hess**: Yes, and a point I should have made is that if you look at the literature, many people talk about changes in mean pulmonary artery pressure, and in fact, we talk about changes in mean pulmonary artery pressure, but the important thing is what the pulmonary vascular resistance is. You need to take the next step and 'shoot' the cardiac output and calculate the resistance because that's really what's important. If the patient has a high mean pulmonary artery pressure because he is septic and his cardiac output's 12 L/min, that means something quite different from the patient who has a high pulmonary artery pressure because of an increased PVR.

**Slutsky**: A comment on your issue about the correct dose. In fact, I think it's in many ways actually quite simple, isn't it? Here you have a drug that gives a physiologic response almost instantly—certainly within a few minutes—and that's how you're going to calculate the dose. There's no reason to have a single universal dose. You just have to decide on a starting dose and then titrate it, as you go. So, I don't think that's a big question. This is a great drug in that respect.

1. Puybasset L, Rouby JJ, Mourgeon E, Cluzel P, Souhil Z, Law-Koune JD, et al. Factors influencing cardiopulmonary effects of inhaled nitric oxide in acute respiratory failure. Am J Respir Crit Care Med 1995;152(2):318-328.

**Hess**: That's a good point. However, we want to make sure that we choose a safe dose as our starting dose and not 100 ppm, so that by the time we get them down to 5 ppm they won't have a methemoglobinemia.

**Slutsky**: Jean Jacques Rouby and his group[1] showed dose-response curves that suggest that most patients respond to nitric oxide at much lower concentrations than 20 ppm and some less than 1 ppm, and yet when you discussed this issue, you kept hinting that you use 5-10 ppm, which I understand from the literature actually is pretty high now. I'm not sure why you're using such high levels, unless it relates to the analyzer you're using.

1. Puybasset L, Rouby JJ, Mourgeon E, Stewart TE, Cluzel P, Arthaud M, et al. Inhaled nitric oxide in acute respiratory failure: dose response curves. Intensive Care Med 1994;20(5):319-327.

**Hess:** Ah, you struck right on it. One of the issues is how Rouby samples inhaled NO. He aspirates gas from the trachea and calls that the inhaled NO dose. He is probably getting a time-weighted average of inhaled and exhaled NO. We've actually looked at some of his work and have modeled some things in the lab. Sometimes where he reports that he is administering 2 ppm, in reality, due to the I:E and what the expiratory NO concentration might be, he may be administering 8-10 ppm. So the doses that he finds effective, I think, are very similar to the doses that we find effective. We're measuring the NO on the inspiratory limb of the ventilator circuit, which is actually what's going to the patient. He's reporting this time-weighted average dose from the gases aspirated from the trachea. Because of the very slow response times of the chemiluminescence analyzers, I don't think that you can aspirate gas from the trachea and call that the inhaled dose—unless you have a device that has a very rapid response to give you almost a capnogram sort of indication of NO.

**Slutsky**: Some devices respond relatively quickly.

**Hess**: Yes. The Sievers device, for example.

**Brochard**: I think the question of the dose is important but not entirely clear. First, I fully agree with you that the way you do the sampling is something that is not easy. Second, I think it raises the question of why we want to use NO in patients and what the objectives are. In fact, there are now several ongoing multicenter studies of NO and ARDS, and I'm not sure that the objectives are really clear. The first one could be to have specific effects of NO at the molecular level, but probably there is no clear hypothesis about that. If that is the case, then we should use other cheaper and less toxic vasodilators because the $PGI_2$ data clearly show that the most important, in my view, is that we administer vasodilator through the airways. Second, possibly we want to use NO because it decreases pulmonary artery pressure. In fact, this was Warren Zapol's first purpose when he proposed that. There are some very preliminary data in animals showing that the decrease in pulmonary artery pressure can be due in part to a decrease in venous pulmonary resistance. Therefore, you can expect a possible decrease in pulmonary edema. But we know from Rouby's data[1] and Gerlach's[2] data that the dose to reduce PAP may be very different from the dose to improve $P_{O_2}$. The third possibility may be that we want to use NO just to decrease $F_{IO_2}$ because we are concerned about toxicity. So it's not so clear to me. A fourth possibility is just to use it as a rescue therapy, as you mentioned.

1. Puybasset L, Rouby JJ, Mourgeon E, Stewart TE, Cluzel P, Arthaud M, et al. Inhaled nitric oxide in acute respiratory failure: dose response curves. Intensive Care Med 1994;20(5):319-327.
2. Gerlach H, Pappert D, Lewandowski K, Rossaint R, Falke KJ. long-term inhalation with evaluated low doses of nitric oxide for selective improvement of oxygenation in patients with adult respiratory distress syndrome. Intensive Care Med 1993;19:443-449.

**Hess**: You bring up a good point, and I want to highlight it. The doses that we talked about here are ARDS doses. As you point out, the doses that are used to lower pulmonary vascular resistance and mean pulmonary artery pressure may need to be higher. So the doses that are used for primary pulmonary hypertension and the doses that I've seen in some of the studies with PPHN are higher doses. But it's a different mechanism.

**Kacmarek**: Just to follow up on that comment—in the Semigran paper where we looked at the effect of NO in patients with severe left-heart failure (these were all transplant candidates), and in subsequent data in patients who were lung transplant candidates, NO at 80 ppm was required to get the maximum response from the pulmonary vasculature. A large dose of NO is really a significant quantity required in any patient with long-term increased pulmonary resistance. Further, just to comment on what Laurent (Brochard) said, the thing that concerns me about NO and its use in ARDS is that none of the data have really provided us with a tracking of how the patient's $F_{IO_2}$ and $P_{aO_2}$ change over time. I believe more and more that we get a response from NO initially that diminishes over time. You turn off the NO and get a rebound, but you get a rebound even in the patient who showed no response the first day. In some patients in whom we start NO today, over the next 2-3 days we may see the $F_{IO_2}$ creeping right back up to where it was prior to the start of NO. So, I really believe it's critical that the outcome studies that are in process be completed before we make any recommendations about the clinical use of NO.

1. Semigran MJ, Cockrill BA, Kacmarek RM, Thompson BT, Zapol WM, Del GW, Fifer MA. Hemodynamic effects of inhaled nitric oxide in heart failure. J Am Coll Cardiol 1994;24(4):982-988.

**Hess**: The way that I think about inhaled NO is it gives you a window of time. If you can do something with that window of time, it might affect outcome, but if you can't, I think you're exactly right. A couple days later you're no better off than you were before. Currently I don't think there's any evidence that NO has any healing effect, per se. Maybe we'll find that it does. Essentially what it does is give you a window of time, so that other therapies can work.

**Masferrer**: I'm curious why you have a patient getting NO for more than 60 days.

**Hess**: That's a good question. The patient whom we had on inhaled NO for 60-some days was actually on very low doses, 1-2 ppm. We tried on several occasions to discontinue it, and the patient had such a severe rebound that we had to put it on again. This was a very sick patient, who even after weeks was still on 60-65% oxygen and, probably 12-15 cm $H_2O$ of PEEP, and was still pretty sick. There was a lot of pressure being brought to bear on the NO team by the primary care physicians to discontinue the NO. Even with turning up the oxygen to, say, 90%, and trying to shut the NO off, the patient had a rebound that made people at the bedside so uncomfortable that we started the NO again.

**Kacmarek**: Just to comment on the extent of the rebound. In the Bigatello study,[1] when we first started doing this, the protocol was to start NO and the next day bring patients back up to 90% oxygen and turn the NO off. Well, 2 of those 14 patients went into ventricular tachycardia when we did that. It was a severe rebound, and these were critically ill patients—some of whom had serious myocardial problems. When we turned off the NO, we had very dramatic rebounds in those patients.

1. Bigatello LM, Hurford WE, Kacmarek RM, Roberts JD Jr, Zapol WM. Prolonged inhalation of low concentrations of nitric oxide in patients with severe adult respiratory distress syndrome: effects on pulmonary hemodynamics and oxygenation. Anesthesiology 1994;80(4):761-770.

**Peruzzi**: Your slide showed that there was a deterioration in oxygenation with NO concentrations greater than 20 ppm. Is that a consistent finding in your experience? If so, to what do you attribute that finding?

**Hess**: No I don't think it is a consistent finding. That was one study—a pretty carefully done study. It certainly has not been our experience (which might mean nothing) that if you go from 10 to 20, that the $P_{O_2}$s drop. However, I think that it does cause one to be careful about using high doses because there is some suggestion in the literature that going to high doses may actually defeat the effect that you're trying to get.

**Slutsky:** Is there any indication that the mechanism by which that occurs is a pulmonary edema? Do they get high wedge pressures?

**Hess**: I don't think so.

**Slutsky**: Do you have any ideas about the mechanism of the rebound effect? Do you think it's down-regulation of endogenous NO-synthase and, thus, there is less endogenous NO produced? If so, that might provide a rationale for weaning NO by decreasing the dose relatively gradually. Sure there might be some patients on 500 ppb (parts/billion) who continue to down-regulate their NO-synthase, and if you go lower slowly you might be able to overcome that problem.

**Hess**: The reason for the rebound is not clear. There may be a down-regulation of NO-synthase. One thing we've considered is phosphodiesterase inhibitors, which, if you think about the biology of NO, it might work. This is an aspect about which a lot of investigation is needed.

**Slutsky:** Have you tried weaning then?

**Hess**: There was a time that we tried to slowly decrease the NO as opposed to just getting to some level and shutting it off. We would end up with these very elaborate systems, where we'd have 2 or 3 blenders in series so we could get down to a quarter of a ppm or a half ppm, and our experience was that those patients, when we took them from a half ppm to none, rebounded just as badly as if we took them from 2 ppm to none. But if you think about it, even 100 ppb of NO is a lot of molecules.

**Slutsky**: That's how much you get from your nose, huh?

**Hess**: Exactly.

# Pressure-Limited Ventilation

Laurent Brochard MD

**Pressure-Limited vs Volume-Targeted Ventilation**
**Settings for Pressure-Limited Ventilation**
  **PCV**
  **Assist-PCV**
  **APRV**
  **PSV**
  **Combinations**
**Goals for Pressure-Limited Ventilation**
  **Control of Peak Alveolar Pressure**
  **Reduction in Barotrauma**
  **Improved Gas Mixing, Oxygenation, & Alveolar Recruitment**
  **Improved Tolerance & Synchrony**
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  **PC-IRV**
  **APRV**
**In Conclusion**

## Pressure-Limited vs Volume-Targeted Ventilation

Pressure-limited ventilation is a form of ventilation in which the target variable, pressure, is held constant during inspiration.[1-3] Forms of pressure-limited ventilation are presented in Table 1. Although a discussion of pressure support ventilation (PSV) comprises part of this paper, the main focus is on the different forms of pressure-controlled ventilation (PCV). For pressure-limited modes, the cycling variable is usually time, whereas flow is the cycling variable only for PSV. Pressure-limited ventilation can be used as a controlled mode of ventilation, in which the trigger variable is time or patient effort. During special situations, a prolonged inspiration is used with pressure-limited ventilation, and it is called inverse-ratio ventilation (IRV). It may also be used as an assisted mode, in which the trigger function is patient effort, as in assist-PCV or PSV. Also, spontaneous breathing can be superimposed on a pressure-controlled setting in which trigger and cycling variables are time. The provision for the patient to breathe spontaneously during the whole mechanical breath makes this mode (airway pressure-release ventilation, APRV, or biphasic positive airway pressure ventilation) unique.[4-9]

The principal difference between PCV and volume-controlled ventilation (VCV) is the absence of a preset tidal volume ($V_T$) with PCV. The volume delivered to the patient is a function of driving pressure and respiratory system mechanics. In case of passive inflation, the driving pressure (the difference between end-inspiratory and end-expiratory alveolar pressure) is a function of the inspiratory and expiratory pressures set on the ventilator, and of (1) the inspiratory time and the resistance to flow, for the inspiratory pressure, and (2) the relationship between the expiratory time and the time constant of the respiratory system, for the expiratory pressure. This last relationship is especially important when pressure controlled IRV (PC-IRV) is used. Indeed, the prolongation of inspiration necessitates a shortening of the expiratory time to the extent that it may not be sufficient to allow complete exhalation. In a monocompartmental system incorporating a single resistance (R) and a single compliance (C), the passive deflation observed during expiration follows a monoexponential

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Table 1. Variations on Pressure-Limited Ventilation in Clinical Use

| Name | Trigger Variable | Limit Variable | Cycling Variable | Special Features |
|---|---|---|---|---|
| Pressure-controlled ventilation (PCV) | Time | Pressure | Time | — |
| PC-inverse-ratio ventilation (PC-IRV) | Time | Pressure | Time | Inspiration is prolonged, with I:E ≥ 1. |
| Assist-PCV | Patient effort or time | Pressure | Time | A back-up respiratory rate is set. |
| Airway pressure-release ventilation (APRV) | Time | Pressure | Time | Spontaneous breathing is superimposed during the whole breathing cycle; the I:E is generally > 1. |
| Intermittent mandatory pressure-release ventilation (IM-PRV) | Patient effort | Pressure | Time or flow | The number of breaths at high pressure and low pressure are set. |
| Pressure support ventilation (PSV) | Patient effort | Pressure | Flow | The pressure rise-time can be adjustable. |

curve, where the time constant is the product R × C. It can be predicted that 3 time constants are necessary for the exhalation of 95% of the inspired $V_T$. Therefore, shortening expiratory time necessarily generates dynamic hyperinflation with, as a consequence, the presence of a positive alveolar pressure at end expiration, also called intrinsic PEEP (positive end-expiratory pressure), or auto-PEEP.[10,11] Therefore during PC-IRV, manipulation of the ventilator settings may have complex effects. These effects have been predicted by mathematical models.[12,13] For example, increasing respiratory rate first increases and then decreases minute ventilation because the rise in auto-PEEP induced by shortening of the expiratory time reduces the driving pressure. Also, changes in oxygenation induced by PC-IRV must be interpreted cautiously by taking into account changes in end-expiratory lung volume.

## Settings for Pressure-Limited Ventilation

### PCV

The set variables are inspiratory and expiratory pressure and both inspiratory and expiratory time or inspiratory time, breathing frequency, and ratio of inspiratory-to-expiratory time (I:E).

### Assist-PCV

An adjustable trigger sensitivity needs to be set in addition to the inspiratory and expiratory pressure. A low breathing frequency may be set as a back-up frequency.

### APRV

During APRV, the same settings are used as for PCV, but the patient is allowed to breathe continuously through the whole breathing cycle. The usual settings include the two levels of pressure and inspiratory and expiratory times. The inspiratory time, which is the time during which the higher pressure is held constant, is generally set much longer than the expiratory time, which is used as a brief release of pressure to increase ventilation.

### PSV

The set variables during PSV are trigger sensitivity and inspiratory pressure above PEEP. On some ventilators the pressure-rise time is also adjustable.

### Combinations

These modes can all be used as forms of synchronized intermittent mandatory ventilation (SIMV), with interposition of spontaneous breaths between pressure-limited breaths. Also, pressure support can be used to assist the spontaneous breaths between volume-controlled or pressure-controlled mandatory breaths, during SIMV.

Lastly, APRV has been modified in such a way that pressure release is synchronized with the patient's expiration, and pressure support can be added during inspiratory efforts. This mode has been called intermittent mandatory pressure-release ventilation.[14,15]

## Goals for Pressure-Limited Ventilation

### Control of Peak Alveolar Pressure

A great concern now exists about the risk of inducing or worsening alveolar lesions by the use of high distending pressures. Indeed, several groups have shown impressive results in animal studies demonstrating that ventilation with high pressure and high volume induces permeability pulmonary edema in animals with previously intact lungs[16,17] or markedly worsens alveolar lesions in previously injured animals.[18,19]

Although the absolute level of lung volume or transalveolar pressure would be a more relevant index of alveolar distention, airway pressure and especially plateau pressure can be used easily at the bedside to estimate the risk of alveolar lesions. One recommendation from a recent consensus conference on mechanical ventilation was to limit this pressure to 35 cm $H_2O$.[20] One easy way to limit the pressure is to use a pressure-limited mode of ventilation.

### Reduction in Barotrauma

It has been claimed repeatedly that the risk of barotrauma may be reduced using PCV because the peak airway pressure is generally reduced in comparison to VCV. This can be a source of great confusion because the peak airway pressure depends on resistive forces, the intensity of which are heavily influenced by the flow of the inflating gas. The flow at end inspiration is much lower in PCV than in VCV, inducing a reduction in peak airway pressure but not, necessarily, in peak alveolar pressure. Therefore, the potential for barotrauma, if any, cannot be reduced simply by reducing the peak airway pressure.

### Improved Gas Mixing, Oxygenation, & Alveolar Recruitment

With PCV, because the flow is decelerating, a different distribution of ventilation may be expected, compared to constant-flow ventilation. This was suggested in COPD patients by Connors and co-workers.[21] The clinical relevance of this phenomenon, however, is probably small in many patients. Valentine and co-workers[22] found little difference among patients in the distribution of ventilation when the effects of SIMV, pressure support, and APRV were compared. Prolonging inspiration, as in PC-IRV, is a supplemental factor that may improve gas mixing. Some animal studies and a few human studies performed in the 1960s and later have suggested that PC-IRV can decrease the ratio of dead space to $V_T$ ($V_D/V_T$) and the level of $P_{aCO_2}$, compared to VCV.[23-25] Although this effect certainly exists, its magnitude is difficult to determine because of a number of drawbacks in these studies: (1) some studies were performed in dogs, which have a high degree of collateral ventilation; (2) the $V_T$ was not always kept constant and therefore, possibly, the level of alveolar overdistention varied; (3) these effects were more pronounced in animals with no or only moderate injury;[23] (4) the range of ventilator frequencies used in some studies was much lower than those currently used.

Many studies found that improvement of oxygenation could be observed with PC-IRV.[26-31] Subsequent well-controlled studies have suggested, however, that this effect essentially resulted from a rise in end-expiratory lung volume due to intrinsic PEEP and to a deterioration of cardiac function when high mean airway pressures were applied.[32-34] Short-term studies keeping PEEP[33,34] or mean airway pressure[35] constant found no significant effect on oxygenation in ARDS or in animal models. One study,[32] however, found that modest manipulation of the I:E could improve oxygenation without worsening hemodynamics or changing end-expiratory lung volume; another claimed that the potential benefit of PC-IRV is time-dependent alveolar recruitment.[29] It has been demonstrated that the effect of PEEP may be gradual and time is needed to 'open the lung.' The same could exist with PC-IRV, which has been suggested in one study.[9] This is, however, difficult to demonstrate and, up to now, no convincing data have demonstrated this phenomenon in patients.

### Improved Tolerance & Synchrony

Improving patient tolerance and/or patient-ventilator synchrony is an important objective proposed for several forms of pressure-limited ventilation.

APRV was initially proposed both as a controlled mode of ventilation and as an assisted mode, with the aim to improve tolerance for the high rise in mean airway pressure associated with continuous positive airway pressure (CPAP). Improvement in cardiovascular function compared to CPAP or controlled ventilation was demonstrated in animals,[36] but few data supporting subjective tolerance have been obtained in patients.

The same mode was also proposed as a means to reduce the amount of sedation given to patients.[9] In an elegant long-term crossover study by Sydow and co-workers,[9] an improvement in oxygenation was observed with APRV, compared to PC-IRV. This change in oxygenation presumably was due to an increase in alveolar recruitment. However, the authors claimed that the amount of sedation was much less during APRV, and this aspect could, of itself, explain changes in oxygenation. It is, therefore, difficult to determine what caused the improvement in oxygenation in this study.

PSV is probably the form of ventilation in which patient tolerance has been studied the most extensively, and the ability of PSV to reduce patient effort has been described in a number of studies.[9,37-39] Assist-PCV is interesting to compare to assist/control because both $V_T$ and inspiratory time can be kept constant and similar in the two modes. In patients in the process of weaning from mechanical ventilation, we compared patient effort or work of breathing during assist-PCV and assist/control ventilation with the same $V_T$ and same inspiratory time.[40] Three situations were studied: (1) In the first, $V_T$ was set high, to 12 mL/kg. In this situation, the drive of the patients was low, and no difference was present in the flow waveform. (2) In the second, $V_T$ was reduced to 8 mL/kg. In this situation a substantially higher level of patient effort was expended during assist/control compared to assist-PCV.

(3) In a third situation, we reduced the inspiratory time in both modes (from 1 s to 0.6 s), thereby markedly increasing peak flow without modifying $V_T$. The difference in work of breathing then disappeared. These data, confirming previous work on the importance of the peak flow setting during assist/control,[41,42] suggest that the peak flow at the beginning of inspiration is probably a major determinant of patient effort. Because pressure-targeted modes always offer a decelerating flow waveform, they advantageously compare with other modes in many situations.

## Results of Clinical Studies

### PC-IRV

Several clinical studies[26-31] have claimed that PC-IRV has the ability to improve oxygenation and decrease peak airway pressure in patients with ARDS, confirming previous animal studies. Most of these studies, however, did not control for end-expiratory lung volume or intrinsic PEEP, did not keep breathing pattern constant, and did not estimate plateau pressure.

The study of Cole and co-workers[32] looked at the effects of prolonging inspiration with an end-inspiratory pause, assessing lung volume by the means of respiratory inductive plethysmography. They found that an I:E of 4 to 1 increased $P_{aO_2}$ but severely depressed cardiac function and oxygen transport. These effects were comparable to the application of external PEEP giving the same end-expiratory lung volume. They also found that only mildly manipulating the I:E up to 1.1:1 or 1.7:1 induced a significant improvement in $P_{aO_2}$ without substantial change in lung volume.

In two comparable well-controlled studies performed in ARDS patients, Mercat and co-workers[34] and our group (Lessard and co-workers)[33] found no benefit of PCV or PC-IRV over VC when total PEEP and $V_T$ were kept constant throughout the study. Changes in $V_D/V_T$ and in $P_{aCO_2}$ were small and not significant, but a significant worsening in oxygenation was observed. These results have been confirmed by Mancebo et al.[43] The two limitations of these studies are their short-term nature and the fact that mean airway pressure was not kept constant.

In a recent animal study by Mang and co-workers,[35] the same comparison was performed at the same level of mean airway pressure. In their sheep model of lung injury, alterations in the ventilation mode or the I:E produced no significant change in hemodynamic, oxygenation, or ventilatory variables.

### APRV

Only a few studies in patients have assessed the efficacy of these modes of ventilation in a controlled manner. Interesting results have been obtained in animal studies suggesting that hemodynamics or oxygenation could be improved by comparison to more classic modes in different models of lung injury.[36] In the study by Sydow et al,[9] an improvement in oxygenation was observed but the mechanism remains difficult to pinpoint. Indeed, this could result from (1) progressive alveolar recruitment over time; (2) the beneficial effect of spontaneous diaphragmatic activity over the whole breathing cycle; or (3) an effect related to the reduction in sedative drugs. Further studies are needed to elucidate the mechanism.

In a well-performed study in patients, APRV was compared to PSV at the same level of mean airway pressure.[44] The work of breathing and the amount of patient effort was compared between the two modes. A higher level of effort was always expended with APRV compared to PSV suggesting that, again, further studies are needed to establish the type of patient that may benefit from APRV.

## In Conclusion

Pressure-limited modes have a limited number of proven benefits and a larger number of suggested but unproved benefits. The proven benefits and the logical rationale for their use are based on the limitation of peak alveolar pressure and on the good patient-ventilator synchrony offered by the decelerating flow of the assist-pressure forms of ventilation.

Suggested but unproved benefits include improvement in gas mixing and distribution of ventilation with inverse-ratio ventilation, at least on a clinically relevant scale. One study does suggest an improvement in oxygenation with only a slight prolongation of inspiration,[32] and the data from another[9] suggest a lessened need for sedation with superimposition of spontaneous breathing on bi-level pressure ventilation.[9] Today, there are only a few clear indications for this mode as a controlled form of ventilation, for ventilating the lungs of patients with ARDS.[45]

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## Brochard Discussion

**Kacmarek**: Laurent, I agree with you 100% about the issue of peak inspiratory flowrate at the onset of the inspiratory phase. What would be interesting, and I don't know of anybody who's done it, is to compare volume-assisted ventilation with a decelerating flow pattern (where you have a *high* peak inspiratory flow and a *reasonable* inspiratory time) to a pressure-targeted mode, either pressure control or pressure support. What is your speculation on whether there would be significant differences if you chose a decelerating flow pattern? I've always felt that it's the flow pattern more than the mode that makes the difference in patients' tolerance and overall work of breathing.

**Brochard**: Well, I'm sure that you are right. It may be very, very close—the two situations—and at least it may be very difficult to find a difference. I don't know whether there would be any difference. Probably if such a study was done, we would have to look for other aspects. One aspect is what has been called synchrony between the patient and the ventilator—timing between the patient's own inspiratory time and the time of the ventilator. Another important aspect, which was not studied, is that an inspiratory time that is too long or the presence of different criteria for cycling from inspiration to expiration may induce expiratory effort. This would also need to be studied, I suppose.

**Hess**: I suspect there are two issues. One is the flow waveform—constant flow versus decelerating flow. I think the other issue might be whether the flow is fixed or variable, and I think that one of the things that you encounter with a pressure mode of ventilation is that the inspiratory flow can vary according to the patient's demand; whereas with volume ventilation, flowrate is going to be fixed—whether it's a constant or a decelerating flow.

**Brochard**: I guess that you are right, but probably when we say that the patient can adapt himself to his own inspiratory flow, this is partially true. For instance, when you impose a pressure on a patient, you impose a certain flowrate and a certain tidal volume. The respiratory rate of the patient reflects this, and the effect of a given pressure level, I think, is probably due essentially to the imposed tidal volume more than to the relief of the load on the muscles. So, it's partially true that we let the patient have his own inspiratory flowrate. Probably the only mode that will do that is proportional assist ventilation, which has other problems and also needs studies.

**Slutsky**: A small question related to inverse ratio ventilation and the study by Cole.[1] You suggested that it should be repeated, measuring auto-PEEP because in that one group there was an improvement. Why do you think that's important physiologically? If you have the same end-expiratory thoracic volume, is it really important whether there was difference in auto-PEEP? Why do you think that's important to reproduce?

1. Cole AG, Weller SF, Sykes MK. Inverse ratio ventilation compared with PEEP in adult respiratory failure. Intensive Care Med 1984;10(5):227-232.

**Brochard**: In fact, in our study, and we never published those data, in our study looking at pressure control inverse-ratio ventilation, in some patients we also looked at an end-expiratory lung volume with the Respitrace, which is very simple in paralyzed patients because you need only one band, so it gives very nice signals, very easy to reproduce. We found a major difference in the information given by the Respitrace and the information given by auto-PEEP. For the same level of auto-PEEP, there was a reduction in the lung volume measured by the Respitrace. So we said "Which one is right? Is it auto-PEEP or is it the Respitrace?" Then we simply disconnected the patient and looked at passive expiratory spirometry, and we found that the FRC or the volume above FRC was exactly the same. So auto-PEEP was right. I suppose this means that the Respitrace also measured a shift in blood volume, which was of major importance, and which can cause a problem in the interpretation of the aerated lung volume.

**Slutsky**: The reason I ask is because there certainly can be differences between the two. Which is more important? Which is a better index of the side effects and the beneficial effects of whatever mode of ventilation? For example, in that Cole study,[1] there was a decrease in oxygen transport and so presumably cardiac output. That's probably related to an increase in pleural pressure, which suggests that probably thoracic volume is more important. So we think about auto-PEEP, but physiologically, which is the most important variable to approximate?

1. Cole AG, Weller SF, Sykes MK. Inverse ratio ventilation compared with PEEP in adult respiratory failure. Intensive Care Med 1984;10(5):227-232.

**Brochard**: You are absolutely right. What I tried to point out is that I think it's very important to understand the mechanism by which it acts because if it is only an increase in lung volume, which was not measured by Respitrace, you can have exactly the same thing with a small level of PEEP. That's what I mean.

**Kacmarek**: I agree that the Respitrace is just not that sensitive an indicator of small thoracic volume changes. We saw the same thing. We published a paper in *Anesthesiology* a few years ago[1] looking at sonomicrometers implanted on the diaphragm in some postthoracotomy patients. We didn't add to that paper the data that you're making reference to, but we used Respitrace and we measured auto-PEEP and we didn't see the change in thoracic volume with the Respitrace, even though we had additional auto-PEEP. I'm just not sure that the Respitrace is sensitive enough to give you those minor changes. It'll tell you changes in pattern, but it is not accurate for identifying changes in total thoracic volume.

1. Fratacci MD, Kimball WR, Wain JC, Kacmarek RM, Polaner DM, Zapol WM. Diaphragmatic shortening after thoracic surgery in humans: effects of mechanical ventilation and thoracic epidural anesthesia. Anesthesiology 1993;79(4):654-655.

**Slutsky:** I don't know that study, Bob. It could have been the opposite problem. It could have been the change in blood volume because the Respitrace is not bad in paralyzed patients, if you calibrate it just before you use it, especially in paralyzed patients because you don't have the problems with changes in degrees of freedom and chest-wall movement. So, it does give you independent information because by measuring auto-PEEP, you have a pressure in the lung, but you don't know what's happened to blood volume in the thoracic cage, and a couple of other things.

**Brochard:** I think that if there are disagreements between the two techniques, the expiration spirometry is something simple—to help you understand where you are and if FRC is the same.

**Peruzzi:** In using pressure-preset modes or pressure-oriented modes in mechanical ventilation of ARDS patients, what do you see as the role of inverse ratio ventilation? Our experience is that we tend to be using more one-to-one or ratios slightly on either side of that. What do you feel about that circumstance?

**Brochard**: Clearly from the literature, except from the Cole study,[1] there are few convincing data showing that pressure controlled inverse-ratio ventilation does something different from increasing intrinsic PEEP. In the initial studies, for instance, I think there were major improvements in oxygenation, which were due both to intrinsic PEEP and to a decrease in cardiac output. This was also shown in the Cole study. So, I don't see a clear place for inverse ratio ventilation, at least at 2 to 1, 3 to 1, or 4 to 1. Another point that is a little bit difficult to discuss is the difference between peak pressure and plateau pressure. Clearly, plateau pressure is much closer to alveolar pressure than peak pressure, but it's not exactly alveolar pressure. To get the best index of alveolar pressure, it would be best to measure the pressure at the exact time when flow comes to zero. So before you have this slow decrease in pressure, you may find some differences between a very high peak flow and a very short inspiration, and a prolonged inspiration, probably because of the distribution of ventilation. But, again, at least in patients, this has not been studied very carefully. But I think this makes sense.

1. Cole AGH, Weller SF, Sykes MK. Inverse ratio ventilation compared with PEEP in adult respiratory failure. Intensive Care Med 1984;10:227-232.

**Kacmarek:** The perspective that we've taken in dealing with inspiratory time lengthening, and I would use that term instead of inverse I-E ratio, is to use it as a mechanism of elevating mean airway pressure (once you've maximized PEEP level from a recruitment perspective) without changing plateau pressure. I think that defines the limit of its usefulness. Once increasing inspiratory time creates auto-PEEP, it becomes no better than any other maneuver used to elevate PEEP. I agree that in most cases an I-E ratio of about 1:1 or a little bit longer inspiratory time is ideal. But, I think it's the philosophical perspective that you come from—if you come from the inverse I-E ratio perspective and jump from 1:2 to 1:1 to 2:1, you can get into real trouble; whereas, if you slowly increase inspiratory time in 0.1 second increments until an oxygenation target is met, the problems that we see in the literature can be eliminated.

**Brochard**: But again I don't think we know if it's necessary to increase mean airway pressure. While it has been said that mean airway pressure is a main determinant of oxygenation, in most studies it's very difficult to separate it from end-expiratory lung volume. For instance, in our study, keeping the same end-expiratory lung volume but increasing mean airway pressure did not improve oxygenation. It even worsened oxygenation.

**Kacmarek**: But I think in your study the reason was that you impaired hemodynamics.

**Brochard**: There was no significant decrease in cardiac output, but there were some trends toward increasing the arterio-venous difference in oxygenation with PCIRV, which suggests that there was some problem in the peripheral oxygenation.

**Kacmarek**: In our experience, by slowly increasing inspiratory time without affecting plateau pressure or without affecting total PEEP, an increase in mean airway pressure of 3-4 cm $H_2O$ clearly improves oxygenation in some cases. But you're right. There's no systematic prospective study that I am aware of that has looked at it from this perspective.

**Brochard**: I think that another point is that, because we use limited-pressure or limited-volume ventilation, we may be at risk in some patients of not fully recruiting available alveoli. This is a possibility. We tried to look at that with CT scan studies, but it's difficult. It's possible that recruitment is not due to PEEP itself but to tidal volume, and PEEP is there to keep the alveoli open. So maybe with small tidal volumes there may be some collapsed regions not reopened. Maybe using intermittent sighs or prolonging inspiration may help in this process, but that is only an hypothesis.

**Slutsky**: I think that is a very important point that we discussed a little bit yesterday in terms of recruitment. If you look at the literature, mean airway pressure appears to be the key determinant of oxygenation, but really it's mean lung volume that's much more important. It's not the only thing but it's much more important. There are some studies that Charlie Bryan has done—I don't know if he's published these, yet—using high-frequency ventilation. The results in relation to $P_{O_2}$ show a hysteresis similar to that of the pressure-volume curve. In other words, oxygen delivery is higher on the descending limb of the $P_{O_2}$ versus airway pressure plot, so at the same mean airway pressure, depending on whether you're on the inflation or deflation limb, you have *huge* differences in oxygenation, from $P_{O_2}$s of 50 to 300. The subject has the same mean airway pressure, but mean lung volume is very different. So, I think we haven't focused on mean lung volume.

That brings up another question, and that is time. A number of anecdotal reports suggest that if you keep people on IRV for a long period of time that they seem to do better. Maybe it's related to recruitment. Maybe it's real or maybe not. I thought you mentioned in your talk that you were going to discuss this a little bit, but I don't remember it coming up.

**Brochard**: No, the only paper, I think, which tried to assess that was the paper by Sydow and Burchardi.[1] Because there are so many differences between the two periods of ventilation, it's very difficult to say whether it's recruitment or not. In their paper they said that there is an improvement in compliance with this mode of ventilation. So, they say that there is a time-dependent recruitment. But if you don't control for sedation, for oxygen consumption, for many things, it's very difficult to interpret.

1. Sydow M, Burchardi H, Ephraim E, Zielmann S, Crozier TA. Long-term effects of two ventilatory modes on oxygenation in acute lung injury: comparison of airway pressure release ventilation and volume-controlled inverse ratio ventilation. Am J Respir Crit Care Med 1994;149(6):1550-1556.

**Kacmarek:** The critical factor—when you look at mean airway pressure as a determinant of oxygenation—is the PEEP level. Independent of PEEP, mean airway pressure only shows a direct relationship to oxygenation when the PEEP is high enough that you're sure that you have recruited all recruitable lung units. Those studies that showed what you're saying all were studies[1] in which PEEP was very low, so that you had some derecruitment during the expiratory period. If you look at Pesenti's[2] data and Gattinnoni's data[3] when they kept PEEP at or above the inflection point, there was clearly a relationship between oxygenation and mean airway pressure, independent of further adjustments in PEEP level. It's a complex inter-relationship and certain things have to occur first, before you can expect that linear change.

1. Cheney FW Jr, Burnham SC. Effect of ventilatory pattern on oxygenation in pulmonary edema. J Appl Physiol 1971;31(6):909-912.
2. Pesenti A, Marcolin R, Prato P, Borelli M, Riboni A, Gattinoni L. Mean airway pressure vs positive end-expiratory pressure during mechanical ventilation. Crit Care Med 1985;13(1):34-37.
3. Gattinoni L, Marcolin R, Caspani ML, Fumagalli R, Mascheroni D, Pesenti A. Constant mean airway pressure with different patterns of positive pressure breathing during the adult respiratory distress syndrome. Bull Eur Physiopathol Respir 1985;21(3):275-279.

**Slutsky:** I agree that the issue is that PEEP is quite often used without full recruitment. In terms of the physiology, really what's important is the recruitment, the lung volume.

**Kacmarek**: Exactly.

**Slutsky:** Once you've opened the lung up completely, …

**Kacmarek:** … then it doesn't really matter how you increase mean airway pressure. If you increase it, you should get a response from oxygenation, whether it's more PEEP, whether it's inspiratory time, whether it's peak airway pressure. Any of those should result in improved oxygenation, *if* you've recruited.

**Hess**: Laurent, you showed the pressure-volume curves that you generate in your ICU, and you had a paper in *American Review* a couple of months ago about this[1]. We actually talked about this a little yesterday—about how in the ICU one can generate those kinds of curves and identify upper and lower inflection points; so, if you could tell us about the system that you use to generate those kinds of curves.

1. Roupie E, Dambrosio M, Servillo G, Mentec H, el Artrous SE, Beydon L, et al. Titration of tidal volume and induced hypercapnia in acute respiratory distress syndrome. Am J Respir Crit Care Med 1995;152(1):121-128.

**Brochard**: OK. In years past we used the super-syringe technique. The super syringe looks like a clyster or a big enema and has the major disadvantage of requiring disconnection of the patient—a major problem in hypoxemic patients. We now use most frequently the technique described by Levy and coworkers,[1] by Ranieri,[2] by Fernandez[3]—a number of papers describing very carefully this technique. The technique is performed during the usual ventilation of the patient by interposing from time to time breaths of different volumes at the same flowrate, being sure at each breath that we have the same volume history, and that we have the same level of end-expiratory volume by measuring intrinsic PEEP. Then we inflate to a very small volume, measure the plateau pressure, come back to the new ventilation, and after 5-6 breaths, inflate to a higher volume and so on. By being sure each time that we start from the same end-expiratory lung volume, we can construct the curve by plotting each pressure-volume point, and the data I presented to you are this type of curve. If you want an inspiratory pressure-volume curve, you cannot see the hysteresis, but to look for the inflection point or the deflection point is very useful. However, as I mentioned, one of the problems with this technique is that it's sometimes difficult to precisely determine the inflection point—probably because you need a large number of points and good accuracy—because it's a very small amount of pressure and some cardiac artifacts simply can change the pressure you measure. So it's sometimes difficult to clearly see the inflection point. That's why I'll say that often in first approximation, we also titrate PEEP just looking at oxygenation on the one hand and hemodynamics on the other hand. The problem with oxygenation is that if you increase PEEP too much, you will see an increase in $P_{aO_2}$ that may be due in part to a decrease in cardiac output. (There is this funny relationship between cardiac output and shunt: decreasing cardiac output, decreases the amount of blood flow to the injured lung.) Of course, it's not very interesting to decrease oxygen transport in these patients. I think that the point where you have an improvement in oxygenation, without worsening hemodynamics, is approximately the same point that you have on the pressure-volume curve. Up to this point, you have only very little hemodynamic effect because the lung compliance is very low. So, the change in lung volume is small, and the hemodynamic consequences are small.

1. Levy P, Similowski T, Corbeil C, Pariente R, Milic-Emili J, Jonson B. A method for studying the static volume-pressure curves of the respiratory system during mechanical ventilation. J Crit Care 1989; 4:83-89.
2. Ranieri VM, Eissa NT, Corbeil C, Chassé M, Braidy J, Matar N, Milic-Emili J. Effects of positive end-expiratory pressure on alveolar recruitment and gas exchange in patients with adult respiratory distress syndrome. Am Rev Respir Dis 1991;144:544-551.
3. Fernandez R, Blanch L, Artigas A. Inflation static pressure-volume curves of the total respiratory system determined without any instrumentation other than the mechanical ventilator. Intensive Care Med 1993;19:33-38.

**Hess:** Very good, because that gets right back to the very first discussion yesterday. We were talking about PEEP and one of the questions asked was whether you titrate according to lung mechanics or according to gas exchange. There was some discussion that maybe the best gas exchange might be very close to the best lung mechanics, which I think you just said.

**Brochard:** Gas exchange is OK, but it is not sufficient. You need to have gas exchange plus hemodynamics—either cardiac output, blood pressure, urine output, or something indicating that you change or your don't change the cardiac output.

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# Noninvasive Ventilation in Acute Respiratory Failure

Laurent Brochard MD

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## Introduction

Noninvasive ventilation has become one of the usual procedures used to support patients with respiratory insufficiency, especially in the home.[1-7] In this report, I discuss exclusively the use of noninvasive ventilation in acute respiratory failure—an application for which its role has not yet been clearly defined. Although some anecdotal experiences and short-term studies have been reported with negative pressure ventilation, I concentrate on modes of positive pressure ventilation because data from controlled trials are available only for these modes.

Although mechanical ventilation is a lifesaving procedure, many complications linked to this technique have been recognized to carry their own morbidity and mortality.[8] The main objective of noninvasive ventilation for acute respiratory failure is to deliver adequate ventilatory support without the need to perform endotracheal intubation. This is different from home mechanical ventilation, where noninvasive ventilation can be used to prevent deterioration of chronic respiratory insufficiency or as an alternative to tracheotomy.[1,9-11] During acute respiratory failure, the main objectives are to avoid complications of endotracheal intubation or to deliver ventilatory support to patients for whom endotracheal intubation is not desirable. Some of those complications result directly from the endotracheal intubation procedure, such as the occurrence of cardiac arrest or aspiration at the time of intubation or laryngeal or tracheal injury with long-term sequelae.[8] Nosocomial pneumonia is often secondary to bacterial colonization of the pharynx and/or upper gastrointestinal tract, with repeated microinhalations of contaminated secretions around the endotracheal tube inducing the development of the pneumonia that is responsible for prolonged hospital stay and mortality.[12] Nosocomial sinusitis is favored by a loss of normal sinus drainage, especially when the tube is placed via the nasal route.[13] The need for heavy sedation and some of the difficulties in weaning or episodes of postextubation respiratory distress may also be attributed indirectly to the presence of the endotracheal tube.

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Another possible indication for noninvasive ventilation is the need to deliver ventilatory support for patients in whom invasive mechanical ventilation is not desirable.[14-16] This can be the case in patients with late-stage disease who refuse to be intubated or in elderly patients with severe underlying chronic diseases. For such patients, noninvasive ventilation may deliver adequate support for respiratory distress at a lower risk of complications. In the same way, because the necessary decisions may be difficult to make at an early phase of acute respiratory failure, noninvasive ventilation may be used to postpone endotracheal intubation.

## Physiologic Effects

### Continuous Positive Airway Pressure

Continuous positive airway pressure (CPAP) has been used for many years in patients with hypoxemic respiratory failure. Improvement in respiratory system compliance leads to a decrease in the work of breathing and an increase in the sense of comfort.[17,18] These effects are combined with an improvement in oxygenation. This type of therapy delivered via a face mask may be poorly tolerated by some patients. CPAP has also been used in patients with left ventricular failure, with the aim of improving both hemodynamics and respiratory mechanics.[19] In fact, acute hypercapnic cardiogenic pulmonary edema is the only condition in which a clear benefit of CPAP has been demonstrated in a randomized controlled trial.[19] In that study by Bersten and co-workers, CPAP significantly improved several physiologic variables and reduced the number of patients requiring intubation.

In the past, CPAP and, more commonly, positive end-expiratory pressure (PEEP) have been considered to be contraindicated for patients with chronic obstructive pulmonary disease (COPD). The main reason was the belief the addition of PEEP had the potential for worsening hyperinflation, a major factor inducing abnormal respiratory mechanics in COPD patients. The description of dynamic hyperinflation in such patients, responsible for a positive value for respiratory system elastic recoil pressure at end-expiration, suggested that such an attitude needed to be questioned.[20,21] When flow limitation is the cause of dynamic hyperinflation, external PEEP may reduce the mouth-to-alveolar pressure difference that exists at the beginning of inspiratory muscle activity and then reduce the inspiratory work of breathing.[20,21] In COPD patients who are not intubated, few data are available on the effects of CPAP. Miro and colleagues[22] used mask CPAP at 5 or 10 cm $H_2O$ in 7 alert, hypercapnic COPD patients. In 5 of those patients, CPAP improved gas exchange but 1 patient was withdrawn because of side effects and was intubated. The small number of patients and the absence of a control group make these results only preliminary.

More interesting seems the combination of CPAP and pressure support ventilation (PSV).[23,24] Appendini and co-workers[24] demonstrated that the combination of these 2 types of ventilatory support in COPD patients who were not intubated had a greater efficacy for reducing inspiratory muscle effort than each one alone. However, in a study by Fernandez and co-workers,[23] low levels of external PEEP could be added successfully to pressure support in only 4 patients of all those experiencing a total of 14 episodes of acute exacerbation of COPD because it generated excessive leaks in the others.

### Intermittent Positive Pressure Ventilation

Both volume-targeted and pressure-targeted modes of intermittent positive pressure ventilation (IPPV) have been used for noninvasive ventilation.[25-27] Assist/control ventilation can be used with usual settings for breathing frequency and inspiratory flow. Because ventilation is volume targeted, any leakage decreases the volume delivered to the patient, and some authors have recommended setting a larger tidal volume than those used in intubated patients.

PSV has also been widely used for noninvasive ventilation.[23,26,28-31] This mode of ventilation usually results in a decrease in the work of breathing, an increased tidal volume, and a reduced spontaneous breathing frequency.[32] During noninvasive ventilation, the presence of leaks are roughly compensated for by the ventilator because the inspiratory pressure is maintained constant. PSV may, however, cause problems in the cycling mechanism from inspiration to expiration based on the flow decay, and some authors have preferred to use assist pressure-control ventilation in which the inspiratory time is preset or to add mechanical volume-targeted breaths using synchronized intermittent mandatory ventilation with pressure support. This problem may also be solved by using an adjustable flow threshold for cycling.[28,29]

In most clinical series, noninvasive ventilatory support has been delivered intermittently.[14,23,26,27,29,31,33-35] For many authors the duration of ventilation was maximal on the first day, from 12-16 hours/day, or even almost continuously with periods of 10-20 minutes during which the assistance was stopped to allow the patient to drink, expectorate, or simply to rest. On the following days, the duration of ventilatory assistance was gradually reduced, depending on the clinical status of the patient. The total duration of ventilatory assistance was remarkably short in most series, ranging from a mean (SD) of 8 (4) hours in the study by Fernandez and co-workers[23] to 3 (1) day in our study reported in 1990,[29] or 4 (2) days in the study by Wysocki and co-workers.[31]

## Mechanisms of Action

### Oxygenation

The first goal of treatment for acute respiratory failure is simply to oxygenate the patient. This raises the problem of interpretation of the uncontrolled studies with apparent benefits of noninvasive ventilation because similar beneficial results may be obtained by ensuring adequate oxygenation, whatever the equipment. In patients with COPD, however, oxygen often worsens hypercapnia and respiratory acidosis, which may constitute a major limitation of standard treatment. By increasing alveolar ventilation, noninvasive ventilation may allow sufficient oxygenation without raising $P_{aCO_2}$.

In some studies, noninvasive ventilation delivered with pressure support was able to improve alveolar ventilation and to decrease $P_{aCO_2}$. In other studies, the main effect on gas exchange was the expected improvement in oxygenation, obtained simply by raising the inspired oxygen fraction, without the subsequent worsening in hypercapnia often reported with oxygen therapy alone.[23,28] This may reflect differences in the severity of patient condition. It is also possible that the assistance could not be delivered in an optimal way in some patients, explaining the failure to rapidly decrease $P_{aCO_2}$. Fernandez and co-workers[23] previously reported that PSV via a full-face mask was able to minimize oxygen-induced hypercapnia in these patients. In patients successfully treated noninvasively, we found that the rate of $P_{aCO_2}$ decrease was much slower than the increase in oxygenation.[28] Therefore, the absence of an immediate drop in $P_{aCO_2}$ does not necessarily indicate a failure of the technique.

### Partial Unloading of Respiratory Muscles

The effects of noninvasive PSV or pressure-limited ventilation on breathing pattern and respiratory muscle activity have been reported in patients with chronic respiratory insufficiency.[29,36,37] Comparable results have been obtained in severe but stable COPD and in patients admitted for acute exacerbation of their disease. Pressure support can be delivered noninvasively and assists each spontaneous breath. It is able to reduce the transdiaphragmatic pressure, the pressure-time index of the respiratory muscles, and the diaphragm electromyographic activity (Fig. 1). This reduction in muscle effort is accompanied by alterations in breathing pattern, with increases in tidal volume, reduction in breathing frequency and, frequently, with an increase in minute ventilation. Oxygenation parameters are improved with a concomitant increase in alveolar ventilation.

In 6 stable hypercapnic patients with COPD, Nava and co-workers[37] showed that improvement in gas exchange was associated with a substantial reduction in diaphragmatic activity

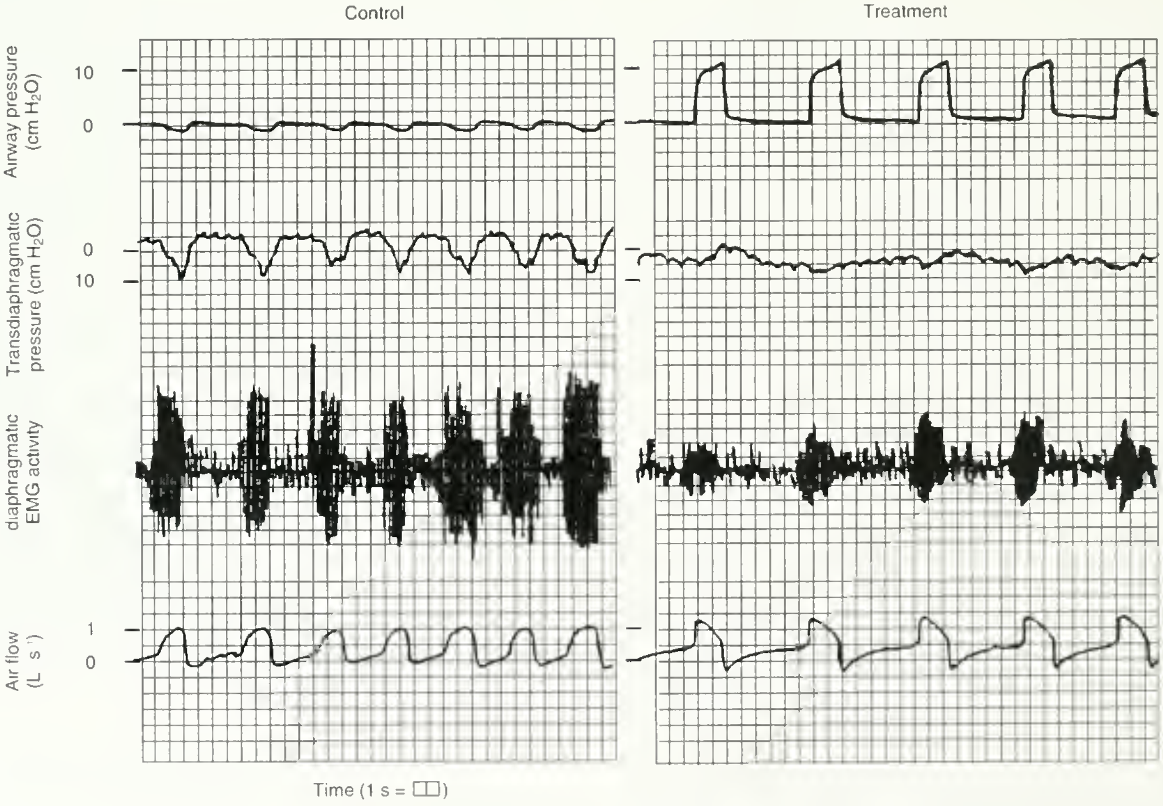

Fig. 1. Tracings of airway pressure ($P_{aw}$), transdiaphragmatic pressure ($P_{di}$), electrical activity of the diaphragm ($E_{di}$) and flow ($\dot{V}$) measured in a COPD patient admitted for acute exacerbation, during baseline (left panel) and during noninvasive ventilation with inspiratory positive-airway pressure (similar to pressure support) (right panel). Note the dramatic reduction in respiratory muscle activity concomitant with modifications in breathing pattern. From Reference 29, with permission.

as reflected by electromyogram (EMG).[37] In a study by Carrey and co-workers,[36] a reduction in diaphragm EMG activity with nasal positive-pressure ventilation was demonstrated in normal subjects as well as in patients with obstructive or restrictive chronic lung disease. In our 1990 study,[29] a reduction in diaphragmatic pressure-time index and diaphragmatic EMG was demonstrated in 9 patients in acute respiratory distress. However, the level of muscular effort did remain substantial in some patients, suggesting that a modest efficacy may be expected in some patients.

The mechanism by which beneficial effects are obtained may, therefore, be a combination of adequate oxygenation and partial unloading of the respiratory muscles, allowing the patient to put his or her muscles partially at rest while keeping alveolar ventilation initially constant.

## Causes of Failure & Influence of Technique

### Side Effects

Complications reported with this technique are usually minor, but they may necessitate its withdrawal. Side effects include skin pressure lesions and facial pain, dry nose, eye irritation, discomfort, poor sleep, mask leakage, and gastric distention. Intolerance of the mask or poor adaptation of the mask to the patient's face may be major limitations to the use of noninvasive ventilation. In a study by Meduri and co-workers,[14] 2 patients among 13 could not be adequately ventilated without major leaks, and therapy was withdrawn. Another patient developed intolerance to the mask after 2 hours of treatment, and, lastly, 2 patients developed mild pressure necrosis at the site of the mask contact, which healed spontaneously in 2 days. Fernandez and co-workers[23] noted no significant side effects except nose pain during 14 episodes of treatment for acute respiratory failure. In a study by Bott and co-workers,[27] of the 30 patients randomized to the noninvasive ventilation, 4 could not be ventilated: 2 because they could not cooperate, 1 because he was unable to breathe through his nose, and 1 because he requested the withdrawal of all active treatment. Comatose patients with a need for airway protection and patients with a frequent need to remove secretions may be difficult to treat with this technique, although such needs do not constitute absolute contraindications.

Gastric distention seems to be uncommon with PSV when mask pressure is limited to 20 cm $H_2O$.[29] Therefore gastric suctioning is not recommended.

An increase in peak pressure augments the risk of leakage and of gastric distention. It also necessitates tightening the mask more closely, with an increased risk of facial lesions.

### Mode of Ventilation

We found that the effects of IPPV were markedly different from those of PSV when delivered to nonintubated subjects with high ventilatory demands. Breathing with IPPV may induce extra work of breathing due to the superimposed impedance of the respiratory circuit and the poor response of the ventilatory device.[38] This emphasizes the importance of the ventilatory mode when ventilatory failure and/or high ventilatory demand are present.

PSV and assist/control ventilation have been the two most frequently used ventilatory modes, with or without combination of PEEP. In one prospective comparative study,[26] pressure support was found to be better tolerated, with fewer side effects. This may be explained by the higher peak mask pressure generated with IPPV and the lower level of comfort in the presence of high peak-airway pressure.

### Patient-Ventilator Interface

In patients with chronic respiratory failure, noninvasive ventilation has usually been delivered through nasal masks.[1] Commercially available models can be used, and high-quality masks in multiple sizes are now available. Customized masks of silicone paste mixed with a slow catalyst can be individually molded to the patient's nose.[5] Masks are secured to the head with straps.

In the acute care settings, many authors are using full-face masks.[23,28,31] Nasal masks, however, present many advantages compared to full-face masks including better comfort for the patient, easier use, and lower internal dead space. During nasal ventilation, however, inadvertent loss of volume through the mouth may cause serious problems. Patients can experience marked patient-ventilator asynchrony during air leakage through the mouth. Carrey and co-workers[36] have shown that during nasal positive pressure ventilation, the position of the mouth is a crucial factor in determining the efficacy of the technique for reducing respiratory muscle activity. Because gas insufflated through the nose may escape largely through the mouth, the closure of the mouth is mandatory. Many patients in acute respiratory failure do not choose to breathe solely through the nose and are often not cooperative enough to do so on request. Disadvantages of the full-face mask are the high degree of discomfort or anxiety generated in some patients, the large internal dead space of the mask, and the difficulty encountered in providing a perfect fit to the patient's face, therefore generating leaks. Manufacturers appear to have made efforts recently to improve the quality of these masks.

We used a specially adapted full-face mask in our studies,[28,29] and it is noteworthy that side effects were few and did not cause withdrawal from ventilatory support in any patient.[24,25] This can probably be explained by the short duration of assistance used in these studies. The use of pressure-limited modes of ventilation allows limiting the peak pressure in the mask, a factor which may play a role in the volume of leaks, the risk of gastric inflation, and the subjective tolerance of the ventilatory support. Also, the motivation and the training of the physicians and other caregivers may play a role in the success rate of the technique.[28,30]

### Mechanical Support Devices

In several recent studies, the possibility has been evaluated of inducing $CO_2$ rebreathing during pressure support using devices initially designed for home mechanical ventilation. Because these systems, delivering 2 levels of positive airway pressure, force the patient to breathe through a single tube, a risk of $CO_2$ rebreathing is present. We[39] evaluated, both experimentally and clinically, the occurrence of $CO_2$ rebreathing during pressure support with a standard BiPAP device (Respironics, Murrysville PA) adjusted at the lowest PEEP and demonstrated that significant $CO_2$ rebreathing occurred, inducing extra work of breathing. This defect can be remedied by using a 3-way valve that adds an additional, but slight, external PEEP. Ferguson and co-workers[40] showed that this side effect of the technique prevented $P_{aCO_2}$ from dropping with ventilatory support in hypercapnic patients.

Also, we recently compared several devices proposed to noninvasively support patients in respiratory failure and found, in a bench study, significant differences in their characteristics.[41] We also demonstrated that these differences had a significant impact on the amount of effort expended by the patients.

## Clinical Results

### Descriptive Studies

Several uncontrolled studies have included patients whose clinical status was severe enough to make the physician estimate that endotracheal intubation was deemed necessary, either immediately or after a few hours of further clinical deterioration. In initial reports concerning noninvasive ventilation, it has been shown that blood gas abnormalities could be partially corrected and that failures—patients who eventually required endotracheal intubation—were most often not related to failure of ventilation itself.[14,25,30,34,42] In an uncontrolled study, Meduri and co-workers[14] described the treatment of hypercapnic respiratory distress in 18 patients, using essentially PSV. In 13 of 18 patients, intubation could be avoided, and the authors noted that the initial 2-hour improvement in $P_{CO_2}$ and pH was a good predictor of the success of the technique (absence of intubation). In addition, in a subgroup of 7 patients, face mask ventilation was applied because postextubation hypercapnic respiratory distress had occurred. Assisted ventilation was delivered noninvasively with the same immediate efficacy as through an endotracheal tube in these circumstances.

Many authors have reported success rates varying from 51 to 87% in hypercapnic patients, most of them having COPD, and similar results were obtained in patients with hypoxemic lung failure. Interpretation of the data obtained in uncontrolled studies is, however, difficult. Wysocki et al[31] assessed the effects of this technique in 17 consecutive patients with various causes for both hypercapnic and hypoxemic respiratory distress. Their overall success rate was 47%. They found that several differences existed between the patients with success and those with failure. Most hypercapnic patients were in the success group, and most hypoxemic patients were in the failure group.

### Nonrandomized Trials with Historical Controls

Vitacca and co-workers[26] compared the clinical efficacy of the 2 main modes of ventilation, (ie, PSV and volume-targeted assist/control ventilation) in a randomized study in 29 COPD patients. The efficacy of the techniques was similar in regard to the need for endotracheal intubation (failure 12% for PSV and 23% for IPPV). It is interesting that the compliance with treatment was better and the side effects were fewer with PSV. These results were compared to an historical control group of patients with disease of comparable or even a lesser degree of severity. They found a significant decrease in the rate of endotracheal intubation with noninvasive ventilation.

In a first study,[29] we reported our initial experience in a series of 13 patients admitted for acute exacerbation of COPD. Results obtained in this group were analyzed in a case-control study, each treated patient being matched with an historical control. A large, significant reduction in the need for endotracheal intubation was observed between the 2 groups (8 vs 85%), associated with a reduction in the length of ventilatory assistance (3 vs 12 days) and in the length of stay in the ICU (7 vs 19 days). All results were highly significant but were obtained in a single center and on a small sample of patients.

### Randomized Controlled Studies

In 1995, Wysocki and co-workers[43] reported the results of a randomized controlled trial comparing noninvasive ventilation to usual care in 41 non-COPD ICU patients with various causes of respiratory failure. Patients with organ failure other than the lungs were not included. On an intention-to-treat basis, no benefit could be demonstrated in terms of need for intubation, length of hospital stay, or mortality. When the subgroup of patients with acute hypercapnic ventilatory failure was examined (including several patients with postoperative and postextubation distress), a significant decrease was found in the need for endotracheal intubation and in the length of hospital stay, with a trend towards a lower mortality. These results indicate that hypercapnic ventilatory failure appears to be a good indication for noninvasive ventilation, whereas the possible benefit of the technique in hypoxemic patients is questionable.

Wysocki et al's results[43] were confirmed in a study with a randomized prospective design by Kramer and co-workers[33] who showed that noninvasive ventilation reduced the need for intubation in patients with acute respiratory insufficiency who were otherwise stable, particularly those with COPD.[29]

In this study, the time spent by nurses and therapists at the bedside was analyzed and was found to be similar whatever the therapeutic approach.

In a randomized controlled study, Bott and co-workers[27] prospectively compared 2 groups of patients admitted for acute exacerbation of COPD. The same medical treatment was applied to both groups, with noninvasive nasal positive-pressure ventilation applied to 1 of the 2 groups. There was a significant improvement in pH from 7.35 to 7.38 in the group treated with noninvasive ventilation, whereas pH fell in the control group after 1 hour. Visual analog scores over the first 3 days of admission showed less breathlessness in the group treated with noninvasive ventilation. Lastly, survival rates were compared in the two groups. In an intention-to-treat analysis, the difference was not significant. However, when the 4 patients who did not tolerate noninvasive ventilation were excluded from the analysis, the mortality rate was found to be significantly lower in the treated group (4% vs 30%, $p < 0.05$).

This experience was recently extended to a randomized trial conducted in 5 European centers.[28] Patients were included in the study when they had been admitted for acute exacerbation of COPD with objective criteria for severity, based on breathing frequency, pH, and $P_{CO_2}$. Patients with a clear and treatable cause for decompensation, such as pneumonia, need for surgery, pneumothorax, acute myocardial infarction, or patients with other organ failure were not included in the study. A total of 83 patients were randomized either to a conventional group for whom treatment included oxygen, antibiotics, and bronchodilators or to a group to whom the same treatment was administered, plus systematic use of noninvasive PSV delivered via a full-face mask. PSV was delivered with a specially manufactured device, designed to have a highly sensitive flow-triggering system, a fast rate of pressurization, and low expiratory resistances (ARM 25, Taema, France). At the time of admission, in the 2 groups while breathing room air, mean pH was ≅ 7.27, $P_{CO_2} \cong 70$ torr, and $P_{O_2} \cong 40$ torr. Although the two groups were similar on admission, a significant reduction in the need for endotracheal intubation was noted: 74% intubated in the conventional group versus 26% in the group treated with noninvasive ventilation. Significant reductions in the length of hospital stay and in the in-hospital mortality (from 29 to 9%) were found. These results were obtained in a carefully selected group of patients (only 31% of all COPD patients admitted in the centers during the study period could be included), but they demonstrated that major benefits can be expected from noninvasive ventilation in the treatment of COPD patients admitted for acute respiratory failure.

## In Conclusion

Noninvasive ventilation may bring considerable benefit for the treatment of acute hypercapnic ventilatory failure, especially in patients with COPD.[27-29,33] Reduction in the need for endotracheal intubation has been demonstrated in selected groups. Several well-controlled studies have also shown that this may be associated with a reduction in the length of hospital stay and in mortality.

A number of failures of the technique have been reported, and further efforts are needed to understand the causes of those. Part of the explanation may come from the equipment used, and improvement in the type of assistance delivered to the patients is clearly needed. New forms of pressure-supported ventilation may bring new benefits.

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## Brochard Discussion

**Peruzzi:** In terms of instituting noninvasive ventilation in a COPD patient, where do you begin this process? We are faced with deciding whether to begin this in the emergency department or in the intensive care unit. Our stance has been to begin it in the intensive care unit because of problems with logistics, personnel, time-intensive titration of ventilatory support outside of an ICU, and transportation to another critical care area. What do you do?

**Brochard:** There are two aspects to this question. One is where to do it. Can we do it outside the ICU? The other question is Should we use it as a preventive measure or just as a support for patients who require immediate ventilatory support? We have no major experience with noninvasive ventilation in the emergency ward. However, some of the groups in our multicenter studies—for instance, the group in Barcelona—decided, for a number of reasons (and one of these reasons was that they had too many patients in the ICU) to use it in the emergency ward, but there are no published data. It seems to work very well, and many patients admitted to the emergency ward with COPD are treated a few hours there, and then get better, and do not need to go to the ICU. This is just an impression. My concern is that it's not an easy technique to apply, and you clearly need to carefully monitor the patient. But this may be done well in the emergency ward, depending on the number of nurses you have and the personnel you have—therapists, physicians—who can be there. So, we don't do it because of a problem of personnel, but probably this can be done if you can monitor your patient closely. The second question is Should we use it very early as a preventive measure—or very late? I think that if we use it very early, the problem is that we will have to administer noninvasive ventilation to a lot of patients. We all know that sometimes we admit patients who we really feel won't require intubation. But if we decide to do it preventively, we should do it in those patients. I think this will cause major problems in the loads imposed on the personnel, and this may also cause some worsening in some patients, who in fact were OK just with oxygen. So I won't recommend doing it very early. However, if you just do it very, very late, this is also difficult. So, we do it in all patients admitted at risk of needing intubation in whom the pH is below 7.35 and who are likely to ultimately require intubation.

**Kacmarek**: Just a comment about the use in the EW versus the ICU. One of the problems we all have if we're not doing noninvasive ventilation under research protocol is the issues that Laurent brought up—personnel, time, education, ability, interest. In application of noninvasive techniques by the general medical community, it's been our finding that the percentage of patients who do well is not as high as you see in the studies. Not that the technique isn't as good, but availability of personnel is a problem. A certain time commitment is required early on in the establishment of noninvasive ventilation, and, of course, it takes a certain personality and commitment to stay with patients and work with them, talk them through it, and make all the modifications. Clearly, practitioners have different capabilities for working with patients. Individuals who are used to working in the ICU and managing ventilators by simply sedating patients and making changes don't do very well in the emergency room talking and working intimately *with* the patient—because it's really the patient who has a lot of the say-so regarding the right settings when you try noninvasive ventilation. There are a lot more complexities in getting a program 'off and going' and working well than meet the eye when you try to begin noninvasive ventilation outside of a research protocol.

**Hess**: In the acutely ill patient, a critical care ventilator does a better job at mask ventilation than some of the bi-level pressure devices. In fact, our approach with the acutely ill patient has been to use an adult critical care ventilator to provide the pressure ventilation rather than to use one of the blower devices. Now, having said that, the issue that comes up is that if one uses pressure-support ventilation, rather than pressure-control ventilation, if there are leaks around the mask, the leak may be greater than the end-inspiratory flow needed to cycle the ventilator. So, my own anecdotal experience has been that many times pressure-control ventilation works better than pressure-support ventilation, just because you can better control the inspiratory time. I think you get better patient-ventilator synchrony in the patient who is actively trying to exhale when the ventilator is still delivering flow because of the leak and so forth.

**Brochard:** That is a very good point. I think, first, that there are clearly differences among the ventilators, and in the study which will be published soon by Lofaso and our group,[1] we compared different bi-level pressure ventilators and there are major differences among those ventilators. In general, I think that those ventilators are very smart for delivering noninvasive ventilation in chronic patients with low ventilatory demand. In the ICU, it's much more a problem. That's why we use a specially designed ventilator to do that, which is close to very good ICU ventilators in terms of pressure support. We think it has other advantages because, for instance, it has very low expiratory resistances compared to classic ventilators with the expiratory circuit. In some patients, it may be beneficial. In fact, we use a combination of pressure support and assist/control because we can fix a maximal inspiratory time on our ventilator. So it's pressure support, but when the cycling level is not recognized, then it stops after a certain time. This time can be set shorter than the usual 3-4 seconds, which is a very long time, so we usually set a 1-second maximum inspiratory time.

1. Lofaso F, Brochard L, Hang T, Lorino H, Harf A, Isabey D. Home vs intensive-care pressure support devices: experimental and clinical comparison. Am J Respir Crit Care Med (in press).

**Mathews**: I am little concerned about using mask ventilation. I can remember back in the 'old days' we worked with mask ventilation for a while and had a lot of problems re-establishing values after we had to take the mask off to do oral suctioning and facial care. We saw a lot of ulcerations of the nose, chin, cheeks, and mouth from pressure from the mask. Have you been running into any of those problems?

**Brochard**: Sure, you can encounter these kinds of problems. My feeling is that compared to what has been done in the past, major improvements have been made in the quality of the ventilatory support and in the type of ventilation delivered. So, those problems that you suggest may be counterbalanced by the beneficial effects of ventilatory support, which are probably much more important. But those are critical points. For instance, the problem of the mask. We now have different types of mask, and in each patient we try to use the best mask. If you want to use masks, you must try them yourself first because some of them are painful on the nose. You have to be very careful about the internal volume of the mask and how it fits the patient. One mask cannot be perfect for all patients.

**Kacmarek**: You noticed, Paul, the picture that Laurent showed about the face mask. One of the things that we have found to be a big problem is that practitioners tend to choose a mask that is too large. They should err on the side of too small rather than too large. You saw Laurent's picture—that mask was fitting half way down the bridge of the nose, which is exactly where it needs to be. If the mask sits any higher, problems with leaks at the top of the mask are significant and, as a result, practitioners strap the mask too tight trying to eliminate the leaks, increasing the likelihood of pressure sores.

**Mathews:** Laurent is right; every patient has to be treated as an individual. No one mask will do it all.

**Peruzzi:** At what point after the acute initiation of noninvasive ventilation do you make decisions about whether just to discontinue it or to continue it on a nocturnal or periodic basis—or to pursue it on a continuous basis at home? How do you decide whether to send somebody home with this? A question I have for Bob (Kacmarek) relates to how one transports a patient on whom you've initiated noninvasive ventilation in the emergency department to an ICU, once it's time to admit them there.

**Brochard:** First, what I may not have mentioned clearly is that this technique cannot be used continuously on a 24-hour basis. This is just an intermittent support. This is important because what we try to do is to do it as long as possible on the first day, maybe close to 20-24 hours. But it's not possible to do that in the days that follow, at least in our experience. So we do intermittent periods, which may be 3 hours or only 1 or 2 hours, and then the same period of rest. Usually weaning is not the problem because when the patient feels better, everybody in the unit is happy to stop the technique. When the patient feels that he really needs the mask, he may ask to go on with noninvasive ventilation. When patients do very well with nocturnal nasal ventilation with a nasal mask, then we discuss the possibility of home mechanical ventilation.

**Kacmarek:** I think Laurent answered it. We begin in the emergency room, stabilizing patients, and then transferring them without ventilation. We put them back on $O_2$ during the transport, and once we get them back to a unit, we re-establish ventilation. I think the big advantage is, as Laurent said, patients can have it off. They can eat, communicate, do mouth care. Even if it's only for 10-15 minutes every couple of hours, it really makes a big difference in their willingness to tolerate this as opposed to all of the other issues that you have when you intubate a patient.

**Peruzzi:** What is the minimum amount of time that you keep them in the emergency department once you've put them on noninvasive ventilation and they're hypercapnic and in difficulty? You obviously don't want to transport them within the first hour. So do you keep them there for several hours, and only then transfer them once you feel that they've stabilized to a reasonable degree?

**Kacmarek:** Meduri[1] has some data showing that patients who are going to do well with noninvasive ventilation will show a clear change in blood gases within the first hour to hour and a half. I think that's your findings, too, Laurent?

1. Meduri GU, Abou-Shala N, Fox RC, Jones CB, Leeper KV, Wunderink RG. Noninvasive face mask mechanical ventilation in patients with acute hypercapnic respiratory failure. Chest 1991;100(2):445-454.

**Brochard:** No. In fact we were surprised in our multicenter study to see that the change in $P_{CO_2}$ in the group successfully treated with noninvasive ventilation was relatively small at 1 hour, and, in fact, was not significant in our study. It only became significant at 12 hours. Our patients improved their $P_{O_2}$ and decreased their respiratory rate, but the drop in $P_{CO_2}$ was much slower. I don't know exactly why because it's a little bit different from our previous findings. We found, initially, that $P_{CO_2}$ went down to a larger extent. This may be due to the design of the study, which was not a study performed in the physiological lab. It was in the ICU with any physician on call. I suspect that some patients were not perfectly fitted with the mask—there were some leaks and some problems.

**Kacmarek:** We transport them when they're reasonably well stabilized. It's a clinical decision made by the group in the emergency room. With some patients, it's quick; with some patients it's a much longer period of time.

**Branson:** I want (especially Bob and, certainly, Laurent) to suggest that somewhere in the near future we make a concerted effort to come to grips with terminology on the devices used to do noninvasive ventilation, because the last time I looked, *all* ventilators were bilevel pressure devices. There's a low pressure and a high pressure. And BiPAP, in America, is a trade name—not a technique. I think a lot of techniques and devices are being misapplied in the ICU as a result of our not being careful with our terminology early on.

**Brochard:** I hope to find that in your book.

**Branson:** It's there!

**Barnes:** Is there a certain segment of this population in whom there's a possibility of gastric insufflation with a variable leak of the mask? If you get a tighter fit than you've had for a while, is there a possibility you'll put air in the stomach?

**Brochard:** Yes. In fact, it has been described, I think, in the study comparing pressure support and assist/control by the Italian group.[1] In the group with assist/control there were some patients with gastric insufflation. Our data and other data clearly suggest that the level of peak pressure in the mask is a major determinant of gastric insufflation. When you go above 20-25 cm $H_2O$ you're at risk of gastric insufflation. That's for inspiration. We also found that adding PEEP and even maintaining the same level of inspiratory pressure also increased in some patients the risk of gastric insufflation. I don't know exactly why the effect of expiratory pressure is different from inspiratory pressure and generates this risk.

1. Vitacca M, Rubini F, Foglio K, Scalvini S, Nava S, Ambrosino N. Non-invasive modalities of positive pressure ventilation improve the outcome of acute exacerbations in COLD patients. Intensive Care Med 1993;19(8):450-455.

**Barnes**: In your experience, has this lead to any significant aspiration pneumonia problems?

**Brochard**: No. In the multicenter study, the number of complications comparing the treated group and the standard-treatment group was significantly reduced, and the number of nosocomial pneumonias was smaller. It was not significant because it came to small numbers. It was maybe 3 pneumonias in the group treated with noninvasive ventilation versus 8-9 pneumonias in the other group, suggesting the reason was endotracheal intubation, probably.

**Hurst**: From a surgical point of view, be careful with gastric insufflation at higher pressures in 3 groups of patients: patients with altered mental status, patients with mid-facial fractures or basal skull fractures, which in itself is going to be an issue, and patients with a fresh esophageal or gastric anastomosis.

**Kacmarek**: But I think Laurent's points are the ones that we need to drive home. Pressure ventilation really doesn't require pressures high enough to cause gastric insufflation. I cannot remember any patient I've personally dealt with for whom we've had to discontinue mask ventilation because of gastric insufflation. I don't think we've had (Dean may correct me if I'm wrong) any patient who's aspirated as a result of noninvasive ventilation.

**Hess**: But I think that is a result of proper patient selection. We have not tried it on the patients Jim's talking about. We think about those kinds of things, and that's why we haven't seen the problem.

**Hurst**: But your experience makes you think about those things, where in less experienced hands that may not be the case.

**Brochard**: I just reviewed some literature on the laryngeal mask, which is something different. I'm not proposing it for noninvasive ventilation, but I was surprised to read that the authors say that 20 cm $H_2O$ was the pressure above which there was a problem of gastric insufflation, thus correlating with our findings.

**Understand.**
**Adapt.**
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# Conference Summary—Mechanical Ventilation: Ventilatory Techniques, Pharmacology, & Patient Management Strategies

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RESPIRATORY CARE Journal Conferences are designed to bring together experts from around the world to present state-of-the-art lectures and papers revolving about a specific topic. The title of the 1995 Conference was, Mechanical Ventilation: Techniques, Pharmacology, & Patient Management Strategies,[1,2] and similar to past conferences, stimulating and provocative presentations were provided by recognized experts. As I sat and listened to each presentation, I could not help but reflect on the historical development of respiratory critical care—how topics considered new and on the cutting edge today have been frequently detailed and discussed in the past. For example, much of what we know about positive end-expiratory pressure, or PEEP, today was described by Alvin Barach in the 1930s and 1940s.[3-5] Alex Adams in his presentation to this Conference pointed out that John Severinghaus described the concept of tracheal gas insufflation (TGI) in the 1960s,[6] and the first use of TGI was documented in 1968.[7] High-frequency ventilation techniques have been available for about 25 years[8] but continue to oscillate between periods of heightened excitement and disappointment regarding clinical utility.[9,10] Regardless of whether anyone is willing to accept the fact that noninvasive positive pressure ventilation (NIPPV) as defined today is simply a refinement of IPPB, the more you examine the historical use of intermittent positive pressure breathing (IPPB), the more obvious become the similarities.[11] With NIPPV we have designed better equipment, refined the patient-ventilator interface, and, with a single purpose for its application, have more appropriately selected patients. Even liquid ventilation has been around since the 1960s.[12] My point is that although the specific applications of these innovations are unique today, repetitive cycles of introduction, acceptance, rejection, and reintroduction are commonly necessary before a management approach becomes a standard of care.

### Protocols for Ventilator Management

The singular presentation that had the most impact on me at this conference was the one presented by Tom East. Tom's presentation focused on the complexity of making decisions in the intensive care unit (ICU) and the sheer numbers of decisions that practitioners must make on a daily basis. He pointed out that an average of 178 clinical decisions are made daily in the ICU, with an estimated 1% error rate, and that of the 1% of decisions made in error, 29% are potentially fatal.[13] Tom also specifically addressed the potential number of decisions regarding mechanical ventilation that are possible. Considering the choices of specific ventilator, mode, oxygen concentration, tidal volume ($V_T$), rate, inspiratory-to-expiratory-time ratio, and so on, and the permutations of these choices, the practitioner has about 37 billion possible decisions that could be made regarding mechanical ventilation.[13] This is clearly an impossible task. Most of us simplify this process by using a specific ventilator and selecting a specific mode and range of variables to be used in defined clinical settings. However, the volume of literature regarding the various aspects of mechanical ventilation continues to grow—seemingly in an exponential manner. With each new piece of literature published or opinion given, the task of the bedside clinician becomes more complex. Even a conference such as this one can increase the complexity of bedside decision making unless the results of the conference simplify the decision-making process. As Tom East has indicated, the most important contribution that experts can make for the practicing clinician is to provide guidelines, establish standards, and define protocols for patient man-

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agement. It is of utmost importance that these recommendations, regardless of the form that they take, be based on data. Respiratory care in general and mechanical ventilation in particular have been driven by anecdote. It is impossible to find a body of literature that defines as a consequence of randomized, prospective studies any aspect of mechanical ventilation. There are no prospective, randomized studies that clearly guide the use of PEEP or that define the mode of ventilation to be used in specific clinical settings. Most recently, a number of clinicians, most notably Laurent Brochard,[14,15] Marcello Amato,[16] Artur Esteban,[17] and their respective colleagues have provided randomized studies, but the number of these is still small.

## Evaluating Techniques & Management Approaches

I propose that we systematically evaluate all new mechanical ventilatory techniques or management approaches based on a rating system that takes into consideration the benefit, ease of application, cost, and potential or real risk to the patient (Table 1). Based on these individual ratings, a summary or overall evaluation of clinical utility can then be established, clearly identifying whether a technology or management approach is experimental and should be applied only under an institutional review board's approved protocol or that the technology or management approach should be considered a standard of care and used by all practitioners (Table 1).

Table 1. A System for Rating Ventilator Technology and Techniques for Ventilator Management

Components To Be Addressed
- Benefit
- Ease of application
- Cost
- Risk

Rating Scale From 1 to 5)
1—Little benefit, difficult to use, high cost, high risk
5—Great benefit, easy to use, low cost, low risk

Overall Rating Totals
5-10—Of little demonstrated clinical use, experimental
11-15—Useful in select patient populations
16-20—Of general clinical usefulness, highly recommended

At this Conference, three central themes dominated the presentations: management strategies,[13-18] ventilation and gas exchange techniques,[6,19-24] and pharmacology.[25-27] In the remainder of this paper, I rate each of the specific aspects of these three categories. However, it should be remembered that these ratings are mine and mine only. They do not represent the consensus of the group and, of course, represent my biases regarding mechanical ventilation and respiratory care in general. I do, however, try to provide support for each of my ratings.

## Management Strategies

In my opinion, the most clinically important discussions at this Conference centered about management strategies during ventilatory support. The global emphasis was that ventilation should always be applied with a *lung-protective* approach. That is, application of mechanical ventilation to all patients should be in a manner that minimizes the potential for causing lung injury. Table 2 lists specific components of mechanical ventilation and my ratings.

Table 2. Rating of Strategies for Ventilator and Patient Management

| Strategy | Benefit | Ease | Cost | Risk | Overall Total |
|---|---|---|---|---|---|
| Minimal PEEP | 5 | 5 | 5 | 5 | 20 |
| Maximal alveolar pressure* | 4 | 5 | 5 | 5 | 19 |
| Permissive hypercapnia | 4 | 4 | 5 | 4 | 17 |
| Prone position | 2 | 2 | 5 | 2 | 11 |

*Transpulmonary pressure gradient

## Minimal PEEP

Figure 1 is an example of a pressure-volume curve of the lung during ventilatory support—a figure typical of the slides shown by several presenters. Note the two components highlighted—the segment that encompasses the lower inflection point and the point of higher inflection. The lower inflection segment represents the minimum level of PEEP necessary in acute lung injury to recruit collapsed lung units. Although data from patients in randomized trials is not available, a number of well-designed animal studies have clearly shown that repetitive opening and closing of lung units at end-expiration can result in injury similar to that seen in acute respiratory distress syndrome (ARDS).[28-30] A 1993 Consensus Statement of the American College of Chest Physicians[31] and results of my polling Journal Conference participants suggests that in early acute lung injury, PEEP should be set above this highlighted range. I consider the application of PEEP in this manner a standard of care in acute lung injury. The question that still has not been adequately addressed is Does PEEP set above the lower inflection range prevent the development of lung injury in human subjects? Data of Pepe et al[32] suggests that the answer is No, but they applied only 5 cm $H_2O$ PEEP, a level below the lower inflection range of most patients.

## Maximal Alveolar Pressure

The management approach that, in my opinion, should be considered a standard of care with all mechanically ventilated patients is limiting the transpulmonary pressure difference to ≤ 30 cm $H_2O$ or—more practically—limiting the peak alve-

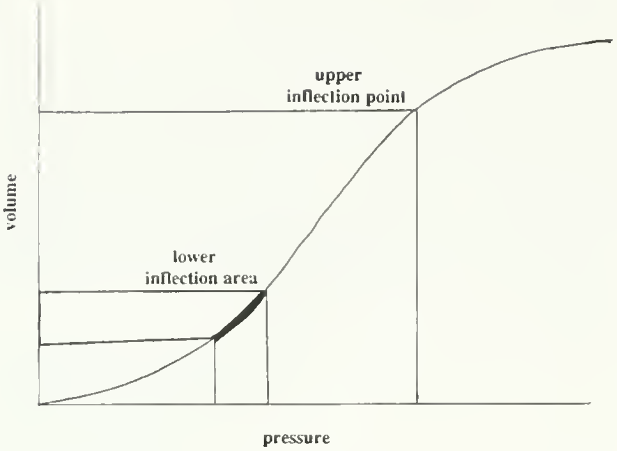

Fig. 1. Pressure-volume curve of the ventilated lung showing the lower inflection area (encompassing the lower inflection point) and the upper inflection point.

olar pressure to ≤ 35 cm $H_2O$. The upper inflection point in Figure 1 represents the pressure and volume at which overdistention of the lung begins. Ventilating above this level in animals has been shown to cause lung injury.[33,34] Unfortunately, much of the available data in patients are from nonrandomized or retrospective studies.[35-37] However, data recently provided by Amato et al[16] have approached significance in outcome in a small group of randomized, prospectively studied patients. The indirect data at this time are overwhelmingly in favor of maintaining peak alveolar (end-inspiratory plateau) pressure below 35 cm $H_2O$. Pressure may exceed this level in patients with reduced chest-wall compliance (those who have ascites, are undergoing peritoneal dialysis, or have received large-volume fluid resuscitation following trauma), but in the majority of patients, it is recommended that pressures be kept below 35 cm $H_2O$.[31]

### Permissive Hypercapnia

If PEEP is maintained at 10 cm $H_2O$ or more and maximal alveolar pressure is 35 cm $H_2O$, little pressure (20-25 cm $H_2O$) is left to ventilate patients with acute lung injury. This has resulted in $V_T$ being set at 8 mL/kg or less in these patients.[31] Rate can be increased to as high as 25/min to maintain minute ventilation, but in all patients, rate increase is limited by auto-PEEP.[37,38] In volume ventilation, auto-PEEP increases the peak alveolar pressure, whereas in pressure ventilation, auto-PEEP decreases the ventilatory pressure difference, reducing $V_T$. As a result, in many patients with acute lung injury, hypercapnia (so-called permissive hypercapnia) must be allowed to develop if targeted alveolar pressures are to be maintained. As addressed by Neil MacIntyre in this Conference,[18] permissive hypercapnia should be considered a standard of care in all settings in which maximal alveolar pressure targets are met. Adverse effects of elevated $CO_2$ are minimal,[39,40] but more concern can be raised regarding pH and the lower limit of acceptable pH in a given patient. It has been my experience, provided no primary cardiovascular or renal problems exist and sepsis is not overwhelming, that most patients are not adversely affected by a pH of 7.20, and in some cases, less. Avoidance of acute reductions in pH can be achieved if hypercapnia is allowed to develop gradually over 24 to 48 hours.[39,40]

### Prone Positioning

Although the subject was addressed in the Discussions but not formally presented at the Conference, I exercise the prerogative of the summarizer and briefly discuss prone positioning in acute lung injury. Prone positioning is not indicated in all patients requiring ventilatory support and is associated with extubation, loss of vascular lines, and hemodynamic stability, but it is indicated in patients with severe oxygenation deficits and ARDS.[41,42] Many have reported dramatic improvements in oxygenation after prone positioning, due to redistribution of blood flow and altered ventilation-perfusion relationships ($\dot{V}/\dot{Q}$).[41-43] Although prone positioning requires careful application, it should be considered part of a lung-protective approach to managing patients with ARDS. I would not at this time consider prone positioning a standard of care but rather a useful adjunct to oxygenation in many patients with ARDS.

### Ventilation-Oxygenation Techniques

The largest group of topics presented at the Conference addressed techniques for assuring optimal ventilation and oxygenation—encompassing the spectrum from highly invasive (extracorporeal gas exchange) to noninvasive (mask ventilation) and from "recommended as a standard of care in all settings" (NIPPV) to "only available under human-subject-approved protocol" (IVOX, or intravascular oxygenation). Individual ratings of these techniques are listed in Table 3.

### Extracorporeal & Intracorporeal Gas Exchange

Three separate techniques—extracorporeal membrane oxygenation (ECMO), extracorporeal carbon dioxide removal ($ECCO_2R$), and IVOX—are currently considered under this heading. It is unfortunate that in adults none of these techniques can be recommended for widespread use. Both ECMO and $ECCO_2R$ have been used with varying success in adults on a limited basis.[44-46] In my opinion, these two techniques should be relegated to regional medical centers where sufficient experience can be accumulated so that the high morbidity and potential mortality associated with these techniques can be minimized. Some still question whether

Table 3. Rating of Techniques for Ventilator and Patient Management

| Technique | Benefit | Ease | Cost | Risk | Overall Total |
|---|---|---|---|---|---|
| High-frequency ventilation (HFV) | 2 | 1 | 1 | 3 | 7 |
| Tracheal gas insufflation (TGI) | 3 | 2 | 3 | 1 | 9 |
| Extracorporeal membrane oxygenation (ECMO) | 3 | 1 | 1 | 1 | 6 |
| Extracorporeal $CO_2$ removal ($ECCO_2R$) | 3 | 1 | 1 | 1 | 6 |
| Intravascular oxygenation (IVOX) | 2 | 1 | 1 | 1 | 5 |
| Airway pressure release ventilation (APRV) | 1 | 3 | 3 | 3 | 10 |
| Extended inspiratory time | 3 | 3 | 5 | 2 | 13 |
| Combined pressure- and volume-controlled ventilation | 4 | 5 | 5 | 5 | 19 |
| Pressure-controlled ventilation (PCV) | 4 | 5 | 5 | 5 | 19 |
| Noninvasive positive pressure ventilation (NIPPV) | 5 | 4 | 5 | 5 | 19 |

ECMO or $ECCO_2R$ should be used in adults.[46] IVOX is highly experimental and, I believe, should be employed only under experimental protocol. Preliminary data make questionable the likelihood of this technique's being used extensively because of cost, difficulty in use, patient risk, and questionable benefits.[47,48]

## High-Frequency Ventilation (HFV)

As mentioned earlier, HFV has been under evaluation for more than 25 years;[6] however, in adults it has never demonstrated efficacy greater than that of conventional ventilation. In pediatrics, reasonable data suggest that high-frequency oscillation be considered an integral part of the care of neonates.[49] Art Slutsky indicated that HFV is the ideal lung-protective approach to ventilation.[23] Pressures generally stay within that narrow band considered acceptable: above minimal PEEP level but below maximal peak alveolar pressure levels. However, when all of the randomized studies previously published are reviewed, outcome with HFV in adults is no different from outcome with conventional ventilation in spite of the fact that conventional ventilation in these studies *was not* performed with lung-protective strategies.[10,50] Pressures and volumes used were clearly greater than those considered maximum targets today. Until HFV can be shown to result in outcomes better than those from conventional ventilation using lung-protective strategies, it must be considered experimental, and in my opinion, should only be used during controlled trials.

## Tracheal Gas Insufflation (TGI)

TGI has been described since the early 1960s,[6,7] yet it has not become a routine component of patient care and no devices designed to apply TGI are commercially available. Recent data[51,52] suggest that TGI may be useful in patients in whom hypercapnia has been allowed to develop; however, the only patient data available to date is in patients with marginal hypercarbia ($\leq$ 60 torr) and normal inspiratory times (about 1.0 s).[53] These patients clearly do not define the sickest population of patients in whom TGI would be most beneficial. In addition, TGI is not without problems. Administration of continuous TGI can result in marked increases in delivered $V_T$, peak alveolar pressure, and auto-PEEP, causing violation of the pressure and volume targets.[54] Expiratory-phase-only TGI overcomes many of these problems, as does volume-adjusted, continuous TGI. However as I noted, there are no commercially available products to administer TGI. Although I consider TGI an exciting potential adjunct to conventional ventilation, it must, at this time, be considered experimental and be used only under strict, experimental protocols approved by institutional review boards.

## Extended Inspiratory Time & Airway Pressure Release Ventilation

I have grouped extended inspiratory time ($t_I$), or inverse I:E, and airway pressure release ventilation (APRV) together because of their similarities. However, I rate their use differently, based on their application. The primary difference between these two is that extending $t_I$ is used in severe ARDS for purposes of oxygenation and is applied to the mechanically ventilated patient who is not initiating inspiration;[55] whereas, APRV has been considered for use in many patient populations, primarily during spontaneous breathing.[56] Of concern with APRV is the patient effort necessary to breathe at an elevated PEEP level (high pressure setting).[38] No data evaluating patient effort during APRV are available at this time (1996). Some data have been published regarding extended $t_I$, all of which shows no improvement in physiologic variables when compared with conventional ventilation at the same PEEP or mean airway pressure.[55,57,58] In spite of this, I recommend the use of extended $t_I$ in ARDS to manage oxygenation, provided no auto-PEEP develops and applied PEEP is set above the inflection range.[57] The reason for this is the effect that extended $t_I$ has on oxygenation without producing an increase in peak alveolar or end-expiratory pressure. Under such conditions, extended $t_I$ fits nicely into a lung-protective approach to ventilation. However, I can only recommend the use of extended $t_I$ in this limited setting when patients are not breathing spontaneously.

### Combined Pressure & Volume-Targeted Modes

Pressure augmentation, pressure-regulated volume control, and volume support combine the beneficial effects of both volume- and pressure-targeted approaches to ventilation. Considering the inability of volume ventilation to target pressure and to provide adequate flow to meet patient demand,[59] these new modes provide an advantageous alternative to classic volume ventilation.[60] It is my interpretation of the literature and of the discussions at this Conference that when available, these modes should be used in preference to volume ventilation. In fact, in future generations of mechanical ventilators, I would abandon classic volume ventilation for a combined pressure- and volume-targeted approach.

### Pressure Control Ventilation

Much literature has been published[55,57,58] and much discussion has occurred regarding pressure versus volume ventilation. However, no definitive advantage has been observed regarding gas exchange, hemodynamics, or pulmonary mechanics during pressure ventilation in acute lung injury. However, pressure ventilation appears to be the ideal mode to use with a lung-protective approach to ventilatory support. First, it allows precise targeting of maximum peak alveolar pressure; and, second, as the lung gets smaller or stiffer, pressure ventilation systematically decreases the $V_T$ while maintaining peak alveolar pressure. Yes, this can be done with volume ventilation, but it requires practitioner intervention. As a result, it is my opinion that pressure ventilation should be considered a standard of care in acute respiratory failure. It is now widely available, cost-effective, easy to use, and without significant risk.

### Noninvasive Positive Pressure Ventilation

I have saved the best for last! The one aspect of ventilatory care that now has significant support from prospective, multicentered, randomized, controlled studies is noninvasive positive pressure ventilation, or NIPPV.[14,61] In the management of the COPD patient in an acute exacerbation, NIPPV must be considered a standard of care. Laurent Brochard's data[14] clearly show benefit for mortality, morbidity, and cost. Although the data regarding its use during extubation are limited, our anecdotal experience suggests that it does have a role in this setting. Figure 2, modified from Elliott and Moxham,[62] shows the role of NIPPV in the management of COPD. NIPPV should be a part of the routine management of COPD patients *in all patient care settings.*

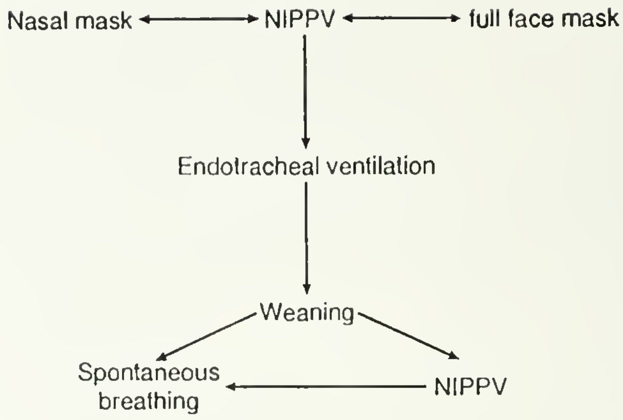

Fig. 2. A flow diagram for the management of the COPD patient in acute exacerbation with NIPPV. (Modified from Reference 53.)

### Pharmacology

Three specific pharmacologic agents were discussed at this Conference: surfactant, perfluorocarbons for partial liquid ventilation (PLV), and nitric oxide (NO). All of these agents show some promise in the management of patients with acute lung injury/ARDS, but all must be considered experimental.[63-65] Each presents with its own unique problems regarding technical application; each is costly; and each is associated with patient risk (Table 4). At this stage in the experimental evaluation of these techniques, it is difficult to determine whether any of them will positively affect outcome. No data to indicate such are available to date. We must await the completion of outcome studies before any of these agents can be considered part of standard care.

Table 4. Rating of Pharmacologic Adjuncts to the Management of Acute Lung Injury and Acute Respiratory Distress Syndrome

| Adjunct | Benefit | Ease | Cost | Risk | Overall Total |
|---|---|---|---|---|---|
| Surfactant | 2 | 2 | 1 | 5 | 10 |
| Partial liquid ventilation | 2 | 2 | 1 | 4 | 9 |
| Nitric oxide | 2 | 2 | 1 | 4 | 9 |

### In Conclusion

The papers associated with this Conference should provide valuable information to guide the clinician in the ventilatory management of a wide spectrum of patients. However, only a few of the techniques discussed (Table 5) should be considered as standards of care to be applied across all institutions in which ventilatory support is provided. At the top of this list is NIPPV, which clearly shows improved outcome. Although I consider them standards of care, the other techniques and management approaches listed in Table 5 are, unfortunately, not supported by the same level of rigorous investigation that supports NIPPV. Finally, the overriding theme of this Conference—which should be the overriding rule for all approaches to ventilatory support—is to always apply mechanical ventilation in a lung-protective manner.

Table 5. Techniques or Management Approaches Considered To Be Standard of Care

| |
|---|
| Noninvasive positive pressure ventilation |
| Lung-sparing approach to ventilatory support |
| Use of minimum PEEP in acute lung injury |
| Use of a maximum alveolar pressure target |
| Use of combined pressure- and volume-targeted approaches to ventilation |
| Pressure control ventilation |
| Permissive hypercapnia |

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# Chest Injury following a Motor Vehicle Crash

Charles G Durbin Jr MD

A 47-year-old obese woman driving a Volkswagen 'beetle' was involved in a head-on collision with a larger automobile at moderate speed (25 miles/h). She was wearing a seat belt but broke the steering wheel in the impact. Her vital signs were stable at the accident scene. She was immobilized on a long spine board and transported by helicopter to the hospital emergency room.

Upon arrival, her vital signs were blood pressure 80/45 mm Hg on her right arm, pulse 122 beats/min, and spontaneous breathing rate of 23 breaths/min. She was complaining of difficulty breathing, but her chest was clear to auscultation. Fluid resuscitation was begun, and tracheal intubation was accomplished to protect her airway. Her vital signs responded to the infusion of fluids, with her pulse declining to 100 beats/min and blood pressure rising to 140/80 mm Hg.

She had a bruise on her lower sternum and was tender to palpation only over the sternum. There was no paradoxical chest movement, and her heart sounds were crisp and clear. No tracheal deviation or neck vein distention was seen. Her right leg was deformed, and she had an open laceration over her right knee. She was awake but sedated and was able to move all extremities and to answer questions by mouthing words and using hand signals. She complained only of pain in her mid-to-upper abdomen and lower chest. Bowel sounds were normal and elicited no guarding or tenderness. Her past medical history included prolonged steroid use for systemic lupus erythematosus.

Blood was drawn for laboratory evaluation and an electrocardiogram was obtained. Her supine chest radiograph is shown in Figure 1.

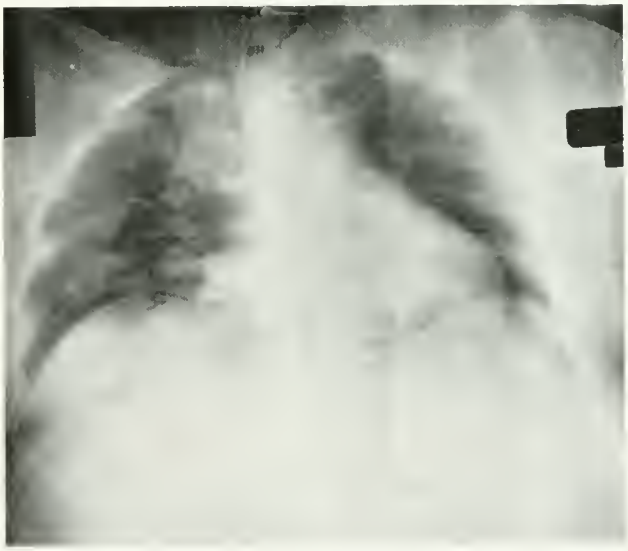

Fig. 1. Supine anteroposterior chest radiograph of obese woman involved in a head-on motor-vehicle collision.

**How would you answer these questions?**

1. What are the radiographic findings? ______________________________

2. What diagnostic procedure is indicated? ______________________________

**Answers and discussion next page**

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**Radiographic Findings.** The anteroposterior (AP) chest radiograph shows the endotracheal tube in good position, lying approximately 4 centimeters above the carina. The heart is large and globular, occupying more than half the thoracic width (normal cardiothoracic ratio is ≤ 0.5[1]). A nasogastric tube is in place, and its tip can be seen just below the diaphragm with no displacement from its usual position. The apical cap in the left lung field suggests pleural or mediastinal bleeding. The mediastinal shadow is wide, and its edge is indistinct; the descending aorta is obscured. Both hemidiaphragms are clearly seen. No rib fractures are apparent but artifacts from the backboard and the patient's brassiere are seen.

The major life-threatening consideration in this patient was the possibility of aortic transection.[2] Untreated traumatic aortic rupture can often lead to a lethal outcome within several weeks of occurrence.[3] Clinical findings in aortic transection include a systolic murmur over the precordium, voice change (from injury or pressure on the left recurrent laryngeal nerve), hypertension in the upper extremities (or different blood pressures in each arm), and weakness and/or hypotension in the lower extremities. Of these, she had only hypertension in the upper extremities. Although no blood-pressure values for her leg were reported, femoral pulses were said to be '4+'—ie, very strong.

Radiographic findings that suggest aortic rupture on an upright posterior-anterior (PA) film include widened mediastinum, blurring of the mediastinal boarder, indistinct aortic knob, rightward deviation of the esophagus, apical capping, downward displacement of the right mainstem bronchus, obliteration of the clear space between the aortic knob and left pulmonary artery, displacement of the left paraspinous margin, and associated first or second rib fractures.[4] Because several of these signs were present on the supine AP radiograph, a more complete diagnostic workup was indicated.

**Diagnostic Techniques.** The usual diagnostic procedure to identify an aortic rupture is an aortic-arch arteriogram; however, ultrasound evaluation and computed tomography (CT) scanning can be sensitive in diagnosing this injury.[5-7] Because her vital signs were then stable, a CT scan of the chest was performed to examine the aorta, with a follow-up arteriogram planned if the results of the CT scan caused any suspicion of aortic tear. Two representative CT images are shown in Figure 2.

A moderate amount of fluid is seen in the right pleural space and a small amount in the left; the aorta is intact; and no pericardial fluid is seen. The CT images show lung tissue herniated into the soft tissues through a traumatic chest-wall defect, between the sternum and rib insertions. When the patient was re-examined, a soft, compressible 10-cm mass could be palpated just to the right of the sternal border. There was no pain or tenderness associated with palpation and no crepitus or evidence of subcutaneous air.

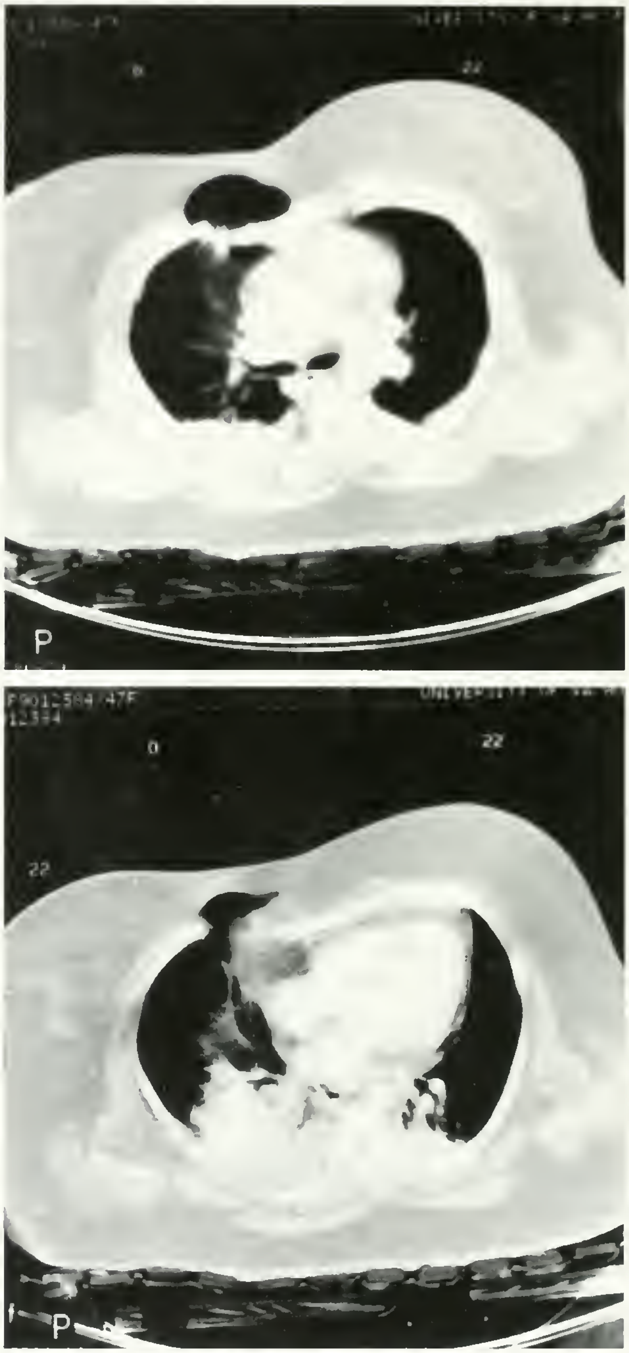

Fig. 2. Two views from a thoracic CT (computed tomography) scan. These images should be viewed as though the viewer were standing at the foot of the patient who is lying in the supine position. The top of the image is the anterior chest wall, and the bottom is the posterior chest wall. On the viewer's right, is the patient's left chest, and on the viewer's left is the patient's right chest.

## Discussion

Herniation of the lung through the chest wall is occasionally seen after thoracic surgery[8-10] or severe coughing[11] but is rare following chest trauma.[12-14] Lung tissue most frequently protrudes through an intercostal space or above the clavicle in the neck. In this patient, the herniation occured through a defect created by sternal-costochondral separation. The major problem resulting from lung herniation is that the lung becomes strangulated and devitalized. This leads to infarction, with loss of gas exchange and the increased potential for infection. Most cases of intercostal lung herniation are treated without surgery. The herniated lung is returned manually into the thorax, and the defect is reinforced with bandages. In severe cases, rib re-approximation is accomplished with sutures, or the defect is obliterated with synthetic material.

Lung herniation is usually a clinical diagnosis. Protrusion of lung tissue is often undetected on routine radiographs.[15] In retrospect, a shadow representing the herniated lung can be seen on the initial radiograph (Fig. 1). This was overlooked by the caregivers and the radiologist during the initial examination, and the patient's obesity made the physical examination less revealing.

Only one other case of post-traumatic, parasternal herniation has been reported in the English-language literature.[7] In both cases, the patients were moderately obese and driving, restrained by seat belts, during the events. Neither patient had significant intrathoracic injury. The herniation was not appreciated on the initial examination or radiograph in either case. In the previously reported patient, the diagnosis was delayed until 10 days after the accident when signs of lung infarction were present, whereas the condition was identified only incidentally on a CT scan in this patient. This may have been due to the fact that the patient was intubated and receiving positive pressure ventilation at the time of the CT scan, thus making the herniated portion of lung larger. Late diagnosis with lung infarction resulted in the need for partial lung resection in the previously reported case. An additional risk factor in the patient reported here was the chronic use of steroids. The connective-tissue-weakening effects of steroid use are well known and may have contributed to the costochondral separation experienced by this patient.

## Treatment

On the second day after the injury, the patient underwent operative exploration. An incision was made anteriorly over the area of herniation. The lung was seen to be viable and was returned to the thorax with aid of lung deflation by the anesthesiologist. The chest-wall defect was closed with wires through the separated rib ends and the sternum. The patient's postoperative course was uneventful. She was weaned from mechanical ventilation within 24 hours, underwent operative repair of a comminuted supracondylar femoral fracture and tibial plateau fracture on the sixth day following injury, and was discharged to a rehabilitation facility on the tenth day. She had no pulmonary complaints and no identifiable residual chest-wall defect when seen in clinic 6 months later. She continues to experience difficulty walking because of the femoral injury.

In summary, this is the second reported case of traumatic costosternal lung herniation. Although the herniated lung was visible on the initial chest radiograph, it was overlooked and later identified on subsequent thoracic CT scan. Treatment was operative reduction and repair of the chest-wall defect. Persons most at risk of traumatic lung herniation may be overweight, seat-belt-restrained drivers involved in head-on collisions. Early detection and repair may reduce the incidence of lung infarction and prevent the loss of lung tissue.

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# Books, Films, Tapes, & Software

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RESPIRATORY CARE, 11030 Ables Lane, Dallas TX 75229-4593.

**Phantom of the Night: Overcome Sleep Apnea Syndrome and Snoring—Win Your Hidden Struggle To Breathe, Sleep, and Live**, Second Edition, by TS Johnson MD and J Halberstadt, with foreword by WC Dement, MD, Chairman of the National Commission on Sleep Disorders Research and Introduction by CE Sullivan, MD. Soft cover, illustrations and graphs, 172 pages. Cambridge MA: New Technology Publishing Inc, 1995. $29.95.

The National Commission on Sleep Disorders Research identified sleep disorders as the number one contributor to the lives and dollars lost secondary to fatigue. Obstructive sleep apnea accounts for a majority of sleepy Americans, approximately 40% of commercial trucking accidents, and the loss of 4,100 lives, 12,000 injuries, and millions of dollars in direct and indirect costs each year. This book is intended to educate those who suffer from obstructive sleep apnea syndrome (OSAS), their families, friends, and employers. Jerry Halberstadt is an OSAS patient who spent many frustrating years undiagnosed and then failed treatment before successfully conquering his apnea. Dr Scott Johnson is a pulmonologist, researcher, and clinician in the field of sleep disorders. Their combination of personal-patient and medical-scientific information make this text appropriate for health-care professionals and the intended lay audience. The Foreword by Dr Dement and the Introduction Dr Sullivan summarize the enormity of the problem of OSAS supported by scientific data from the National Commission on Sleep Disorders Research. Dr Sullivan's comments about his mother's snoring and death preview the book's personal focus: "In July 1967, I was awoken by the silence at 5:00 AM. It was rare for me to awaken so early. I found her dead."

Chapter 1, "Learning to Breathe, Sleep, and Live," is a patient-to-patient discussion of Mr Halberstadt's struggle to function before diagnosis, his challenges after diagnosis, and finally his recovery. He does not belabor the 'poor me' aspect but states facts, lists his symptoms, discusses the consequences of remaining untreated, and defines barriers to successful treatment. He communicates to the intended readers in the first person. He prefaces each succeeding chapter with a personal note and anecdotes relating to the subjects covered. Chapter 2 defines normal sleep and sleep staging in layman's terms. Chapter 3 not only defines disrupted sleep usually associated with OSAS but also provides a questionnaire for readers to assess their sleepiness/fatigue and potential for sleep apnea. The authors reprint the questionnaire on page 167 and give permission for it to be reproduced and used for "anyone who may have sleep apnea syndrome." Chapter 4 identifies anatomic and physiologic aspects of OSAS and the medical consequences of untreated OSAS and snoring.

Readers who work in sleep centers and frequently encounter patients who have no idea what to expect will be pleased with Chapter 5, "Testing How You Sleep." It explains procedures used in polysomnography. The average, sleepy OSAS patient may have difficulty reading all of this chapter, but the patient is likely to still be more informed than most patients entering the sleep center or being studied at home. Each variable commonly recorded during polysomnography (ie, brain waves, airflow, effort, heart beat, oxygen) is described in the text and illustrated graphically. Students and technologists who are considering working at a sleep center and physicians who have not visited a sleep center will find this chapter enlightening. A summary of the individual descriptions of recorded variables with a drawing or photo of a patient fully prepared for a sleep study might strengthen this chapter.

The "symphony of sleep" is a good metaphor for the sleep cycles normally present in a healthy individual and is used well in Chapter 6, "Understanding Your Sleep Report," to explain the "discord" of sleep disrupted by OSAS. Again, as in the previous chapter, the reader/patient may have difficulty with the graphics, particularly the histograms, but they are well supported in the text and the health-care practitioner will find this a good introduction to the reporting formats of sleep pathology and particularly OSAS. Chapter 7 describes continuous positive airway pressure (CPAP) and how it works. It also explains bi-level ventilation, ramping, and other techniques. Appendix D supports this chapter with actual photographs of several nasal CPAP units and mask/nasal pillow options and a chart showing various options for several makes and models of CPAP and bi-level units. Chapter 8, "Making CPAP Work for You," is probably one of the most important chapters in the book from a patient's point of view. It discusses most of the practical issues and problems associated with nasal CPAP use. Perceived difficulty and inconvenience of travel with a nasal CPAP unit can encourage noncompliance. This chapter does a good job of explaining the many issues and solutions to OSAS involved in everyday life, including a chart to calculate battery usage while camping. Appendix B supplements this chapter with an information card and emergency medical card, which readers are given permission to copy and carry with them. This card might be provided to patients by home care companies and physicians because it documents positive airway pressure treatment type and prescribed pressure, which patients rarely remember when admitted for surgery or emergency care. Other common medical and practical issues associated with nasal CPAP use are discussed, including tips on how to deal with insurance companies. Because costs can be a strong factor in noncompliance, this is a worthwhile inclusion. Other options for treatment are discussed in Chapter 9, and Chapters 10 and 11 are summarized with action plans to assess sleepiness and potential for OSAS, seek diagnosis and treatment, assess recovery, and find support.

Appendix A is a directory of organizations, manufacturers, and home care companies. Readers are encouraged to photocopy Appendix B and provide it to their health-care providers. The appendix describes special considerations of airway management in treating a patient with OSAS and provides the patient with indications, such as the placement of an intravenous line so that sedation may be used and information about sedatives that may compromise the airway during certain procedures. The permission to photocopy the Appendix and provide it to health-care professionals reinforces this book's repeated encouragement for patients to take an active role in their care and treatment.

The four-page bibliography contains a wealth of references for both the patient and professional reader who wish to continue education in sleep medicine. The index and glossary provide easy references for patients progressing through diagnosis and treatment and may be used to review sections that parallel a patient's specific needs. The health-care professional seeking to provide information and support to a patient may also find the index and glossary helpful. Internet and World Wide Web information sources are listed for up-to-date information and interaction.

As a health-care professional working in sleep medicine for more than 10 years, I can intimately identify with the 'black hole' of knowledge about fatigue and, particularly, the identification, treatment, and follow up of OSAS patients. Patient/author Halberstadt best states this book's purpose in Chapter One.

> Our mission is to help bridge the gap between scientific medicine and the people whose lives it could transform. The purpose of this book is to help you, the reader, work with your doctor to determine if you have sleep apnea syndrome, to obtain a diagnosis, and to seek treatment and rehabilitation using appropriate medical, professional, personal, family, and community resources.

The text is easy to read for the average patient. Although well above the fifth grade reading level suggested for patient education material, **Phantom of the Night** accomplishes its mission. It covers the primary aspects of diagnosis and treatment of OSAS and the risks associated with remaining untreated. Health-care professionals will find it equally easy to read and will likely glean more from the scientific writings, graphs, and charts than the lay reader. There is more scientific, clinical, and practical information for the health-care professional in **Phantom of the Night** than is provided in all but a small percentage of medical, respiratory, and nursing schools. As the title suggests, OSAS is insidious and frequently unrecognized and untreated. Sleepy OSAS patients endanger themselves and others. I suggest **Phantom of the Night** as required reading for all respiratory care practitioners (RCPs) and primary care and pulmonary physicians who do not already possess extensive training in sleep medicine. RCPs cross-training in sleep centers and home care, graduate RCPs, and RCP and nursing students will find this inexpensive text equally helpful and likely recommend it to patients. The book would be a good addition to physician and sleep center libraries and waiting rooms. The questionnaire, emergency information cards, and other forms which readers are encouraged to copy could become useful educational and diagnostic tools.

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**Respiratory Illness in Children** by PD Phelan, A Olinsky, and CF Robertson. Hardcover, illustrated, 414 pages. Oxford, Blackwell Scientific Publications, 1994. $125.

**Respiratory Illness in Children** is a fourth edition publication. The authors clearly state that their aim is to "...present a comprehensive account of illnesses affecting the respiratory tract of children..." placing emphasis on "...epidemiology, physiology and psychosocial factors in the disease." They have met their goals in this well-referenced book covering many illnesses and diseases affecting pediatric patients.

The initial chapter is a comprehensive review of lung growth and development. The authors use illustrations to expound the topic. Chapter 2 on neonatal lung diseases cover several distinct illnesses from meconium aspiration to persistent fetal circulation. The authors include individual sections on clinical presentation, management, clinical findings, and radiographic appearance as warranted by each particular disease. Radiographs to illustrate different patterns of disease are included not only in this chapter but throughout the book.

The next three chapters review not single diseases, but five clinical categories that are identified and covered individually. These are upper respiratory tract infection, croup and epiglottitis, acute bronchitis, acute bronchiolitis, and pneumonia. The authors thoroughly cover infecting agents, host factors, and environmental factors. In addition, this chapter discusses respiratory illnesses and prevention in developing countries. The next chapter presents the same illnesses, this time from a clinical perspective, including diagnosis, management, and etiology. The division of the information regarding the same disease into two separate chapters is somewhat difficult to follow and forces the reader to look in more than one area for complete information regarding a particular disease.

I especially enjoyed the chapter on respiratory noises. The authors divided the chapter into distinct respiratory noises and presented diseases as they relate to the sounds. Wheezes are explained by pathophysiology. The authors cover the clinical significance of wheezes in several illnesses, such as acute viral bronchiolitis, asthma, obliterative bronchiolitis, foreign body, tracheomalacia, and tracheal webs. The authors do an excellent job of illustrating 'all that wheezes is not asthma,' by covering many other potential sources of wheezing. The pathophysiology of stridor incorporates several anatomic defects including hemangioma of the larynx, foreign bodies, laryngeal webs, and tracheal stenosis. The authors treat and explain each as an individual entity covering everything from management to treatment options.

Asthma generated two distinct chapters in this reference book, one on pathophysiology and epidemiology and a second chapter on clinical patterns. Both chapters are informative and logically arranged. Under pathogenesis, the author reviews allergen exposure, exercise-induced bronchospasm, viral infections, nocturnal asthma, and weather-induced wheezes. Clinical patterns and complications are discussed and a detailed section included on the management of the child and his family, emphasizing that treatment may involve more than just the patient. Formal education warranted only one paragraph and emphasized the role of the physician in the education of the patient and family.

The only other single disease that merited a complete chapter is cystic fibrosis. Because it is a disease that impacts many organ systems, the devotion of a complete chapter was a logical decision. The authors do make a point that the treatment of this diseases is best handled in a multidisciplinary team approach. Because I work closely with the local Cystic Fibrosis Clinic and am involved in family education and support in addition to the diagnositic testing of patients in our clinic, I would like to see respiratory therapists listed as integral members of the team. On page 208, the authors include a concise table of organ involvement in CF that provides a good summary of organs, pathogenesis, clinical manifestations, onset, and frequency, making it an excellent general guideline and overview for health-care professionals not familiar with cystic fibrosis. I was disappointed in this chapter because it did not address the flutter valve—a technique our center has found valuable.

This is a book on respiratory diseases, and I commend the authors for including the manifestations of cystic fibrosis on the other important organ systems. They covered gastro-intestinal complications thoroughly. The authors also had the insight to cover two other important therapies now offered to patients with cystic fibrosis: lung transplantation, increasing in popularity, and DNase, a new pharmacologic therapy. The authors covered the current research in gene therapy and their thoughts about the increasing survival rates of cystic fibrosis patients.

A complete chapter is devoted to tuberculosis. Many radiographs and diagrams showing distinct patterns of involvement are contained in this section. Pharmacologic therapy is also extensively covered. The chapter on lung involvement in human immunodeficiency virus (HIV) was written by Robert B Mellins MD and Walter E Berden MD. The authors included many radiographs and CAT-scans to show the disease patterns in HIV infection. The final two chapters were devoted to tumors and congenital malformations. Very precise drawings and radiographs were contained in this chapter.

The chapter on sleep-related disorders was short but concise. The authors managed to cover the physical defects and their impact on physiology. Nasal continuous positive airway pressure therapy was presented in this chapter. A good deal of information was included on alveolar hypoventilation, and particularly congenital central hypoventilation syndrome. The authors discussed long term mechanical ventilation options and presented the pros and cons for negative- versus positive-pressure ventilation. Impact on the family unit in terms of increased care and emotional costs were also covered.

Overall this is a concise and complete reference manual on pediatric respiratory illnesses. It is fairly easy to read despite the fragmentation of information related to individual diseases that was spread throughout different chapters. Many useful graphs, illustrations and photographs are presented. I especially enjoyed the chapters on sleep related disorders and respiratory noises. This reference book would be a useful addition to any library.

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# New Products & Services

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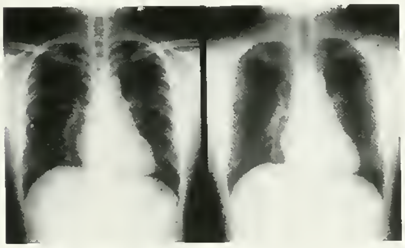
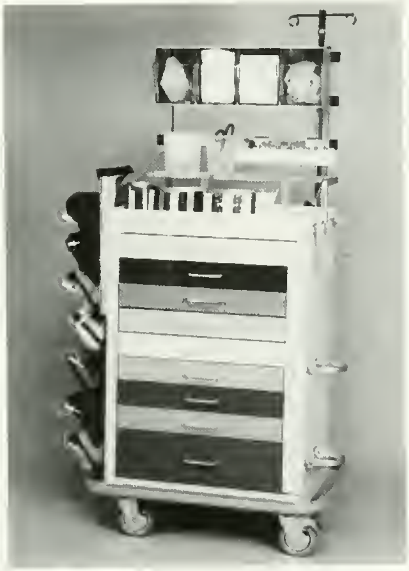
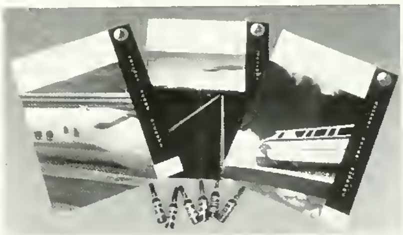


**RADIOGRAPHIC TECHNOLOGY.** Fuji Medical Systems U.S.A. Inc introduces the FCR 9501ES upright image reader that combines energy subtraction technology and computed radiography. The new reader allows physicians to see either bone only or tissue only and a standard digital x-ray. Fuji claims that the energy subtraction unit uses 2 imaging plates separated by a copper filter to capture both low-energy and high-energy image signals in a single exposure. A subtraction process and a noise reduction algorithm are used to provide the different images. In addition, the reader can process up to 120 imaging plates/hour. The unit provides rapid image capturing and the possible elimination of repeat exams while potentially reducing the radiation dose for patients. For details from Fuji Medical Systems, circle reader service card number 187.



**PEDIATRIC EMERGENCY CART.** Armstrong Medical Industries Inc releases A-SMART® COLORCODE® Pediatric Emergency Cart. According to Armstrong, the cart's 9-drawer design features a color code that correspond to the Broselow/Hinkle™ Pediatric Emergency System, a system that organizes pediatric equipment according to the weights and sizes of pediatric patients. The cart also has a breakaway lock, ball-bearing drawers, a seamless plastic top, 5-in. all-swivel casters, ergonomic push handles, and a full wrap-around rubber bumper. Circle number 188 for more information about this cart from Armstrong Medical.

**MINIVAN.** Independent Mobility Systems Inc introduces the new wheelchair-friendly minivan—Rampvan™. The Rampvan is a Ford Windstar or a Chrysler minivan converted for people who use wheelchairs. According to the manufacturer, the van has undergone the most thorough crash and safety testing in the industry. The van has a kneeling suspension for a better ramp angle; an automatic door; quick entry and exit controls on the dashboard, inside the door, and right-rear quarter panel; a low floor for better headroom; exchangeable and removable front seats; and 4 interior wheelchair tie-down positions. The ramp folds out of the way, swings open for nonwheelchair passengers, acts as a safety-gate, and senses obstructions and stops until clear. Other options are available. Circle reader service card number 189, for details from Independent Mobility Systems.



**BLOOD GAS QUALITY CONTROL PROGRAM.** Radiometer America Inc releases *On Track with Quality Control*—a literature package describing the clinical rationale behind blood-gas quality control and related procedures. The information is divided into 3 booklets. The first booklet, according to Radiometer, explains the clinical background for quality control and the need to implement a well-functioning quality assurance program. The second describes an easy-to-use and easy-to-implement quality assurance program for blood-gas analyzers. The third booklet introduces several tools available from Radiometer for using the system. For copies of the booklets, circle Radiometer America's reader service care number 190.

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# Manuscript Preparation Guide

## General Information

RESPIRATORY CARE welcomes original manuscripts related to respiratory care and prepared according to these Instructions. Manuscripts are blinded and reviewed by professionals who are experts in their fields. Authors are responsible for all aspects of the manuscript and receive galleys to proofread before publication. Each accepted manuscript is copyedited so that its message is clear and it conforms to the Journal's style. Published papers are copyrighted by Daedalus Inc and may not be published elsewhere without permission.

Editorial consultation is available at any stage of planning or writing. On request, specific guidance is provided for all publication categories. These Instructions and related materials are available. Write to RESPIRATORY CARE, 11030 Ables Lane, Dallas TX 75229-4593, call (214) 243-2272, or fax (214) 484-6010.

## Publication Categories & Structure

**Research Article:** A report of an original investigation (a study). It includes a Title Page, Abstract, Introduction, Methods, Results, Discussion, Conclusions, Product Sources, Acknowledgments, References, Tables, Appendices, Figures, and Figure Captions.

**Evaluation of Device/Method/Technique:** A description and evaluation of an old or new device, method, technique, or modification. It has a Title Page, Abstract, Introduction, Description of Device/Method/Technique, Evaluation Methods, Evaluation Results, Discussion, Conclusions, Product Sources, Acknowledgments, References, Tables, Appendices, Figures, and Figure Captions.

**Case Report:** A report of a clinical case that is uncommon, or was managed in a new way, or is exceptionally instructive. All authors must be associated with the case. A case-managing physician must either be an author or furnish a letter approving the manuscript. Its components are Title Page, Abstract, Introduction, Case Summary, Discussion, References, Tables, Figures, and Figure Captions.

**Review Article:** A comprehensive, critical review of the literature and state-of-the-art summary of a pertinent topic that has been the subject of at least 40 published research articles. Title Page, Outline, Introduction, Review of the Literature, Summary, Acknowledgments, References, Tables, Appendices, and Figures and Captions may be included.

**Overview:** A critical review of a pertinent topic that has fewer than 40 published research articles.

**Update:** A report of subsequent developments in a topic that has been critically reviewed in this Journal or elsewhere.

**Point-of-View Paper:** A paper expressing personal but substantiated opinions on a pertinent topic. Title Page, Text, References, Tables, and Illustrations may be included.

**Special Article:** A pertinent paper not fitting one of the foregoing categories may be acceptable as a Special Article. Consult with the Editor before writing or submitting such a paper.

**Editorial:** A paper drawing attention to a pertinent concern; it may present an opposing opinion, clarify a position, or bring a problem into focus.

**Letter:** A signed communication about prior publications in this Journal or about other pertinent topics. Tables and illustrations may be included. Mark "For publication."

**Blood Gas Corner:** A brief, instructive case report involving blood-gas values—with Questions, Answers, and Discussion.

**Drug Capsule:** A mini-review paper about a drug or class of drugs that includes discussions of pharmacology, pharmacokinetics, and pharmacotherapy.

**Kittredge's Corner:** A brief description of the operation of respiratory care equipment—with information from manufacturers and editorial comments and suggestions.

**PFT Corner:** Like Blood Gas Corner, but involving pulmonary function tests.

**Cardiorespiratory Interactions.** A case report demonstrating the interaction between the cardiovascular and respiratory systems. It should be a patient-care scenario; however, the case—the central theme—is the systems interaction. CRI is characterized by figures, equations, and a glossary. See the March 1996 issue of RESPIRATORY CARE for more detail.

**Test Your Radiologic Skill:** Like Blood Gas Corner, but involving pulmonary medicine radiography and including one or more radiographs, may involve imaging techniques other than conventional chest radiography.

**Review of Book, Film, Tape, or Software:** A balanced, critical review of a recent release.

### Preparing the Manuscript

Print on one side of white bond paper, 8.5 in. x 11 in. (216 x 279 mm) with margins of at least 1 in. (25 mm) on all sides of the page. Use ***double-spacing*** throughout the ***entire*** manuscript. Use a standard font (eg, Times, Helvetica, or Courier) at least 10 points in size, and do not use italics except for special emphasis. Number all pages in upper-right corners. Indent paragraphs 5 spaces. Do ***not justify***. Do ***not*** put authors' names or other identification anywhere except on the title page. Repeat title only (no authors) on the abstract page. Begin each of the following on a new page: Title Page, Abstract, Text, Product-Sources List, Acknowledgments, References, each Table, and each Appendix. Use standard English in the first person and active voice.

Center main section headings on the page and type them in capital and small letters (eg, Introduction, Methods, Results, Discussion). Begin subheadings at the left margin and type them in capital and small letters (eg, Patients, Equipment, Statistical Analysis).

**References.** Cite only published works as references. Manuscripts accepted but not yet published may be cited as references: designate the accepting journal, followed by (in press). Please provide 3 copies of the in-press article for reviewer inspection. Cite references in the text with superscript numerals. Assign numbers in the order that references are first cited. On the reference page, list the cited works in numerical order. Follow the Journal's style for references. Abbreviate journal names as in *Index Medicus*. List all authors.

Article in a journal carrying pagination throughout volume:

1. Rau JL, Harwood RJ. Comparison of nebulizer delivery methods through a neonatal endotracheal tube: a bench study. Respir Care 1992;37(11):1233-1240.

Article in a publication that numbers each issue beginning with Page 1:

2. Bunch D. Establishing a national database for home care. AARC Times 1991;15(Mar):61,62,64.

Corporate author journal article:

3. American Association for Respiratory Care. Criteria for establishing units for chronic ventilator-dependent patients in hospitals. Respir Care 1988;33(11):1044-1046.

Article in journal supplement: (Journals differ in their methods of numbering and identifying supplements. Supply sufficient information to promote retrieval.)

4. Reynolds HY. Idiopathic interstitial pulmonary fibrosis. Chest 1986;89(3, Suppl):139S-143S.

Abstract in journal: (Abstracts citations are to be avoided. Those more than 3 years old should not be cited.)

5. Stevens DP. Scavenging ribavirin from an oxygen hood to reduce environmental exposure (abstract). Respir Care 1990;35(11): 1087-1088.

Editorial in journal:

6. Enright P. Can we relax during spirometry? (editorial). Am Rev Respir Dis 1993;148(2):274.

Editorial with no author given:

7. Negative-pressure ventilation for chronic obstructive pulmonary disease (editorial). Lancet 1992;340(8833):1440-1441.

Letter in journal:

8. Aelony Y. Ethnic norms for pulmonary function tests (letter). Chest 1991;99(4):1051.

Paper accepted but not yet published:

9. Hess D. New therapies for asthma. Respir Care (year, in press).

Personal author book: (For any book, specific pages should be cited whenever possible.)

10. DeRemee RA. Clinical profiles of diffuse interstitial pulmonary disease. New York: Futura, 1990:76-85.

Corporate author book:

11. American Medical Association Department of Drugs. AMA drug evaluations, 3rd ed. Littleton CO: Publishing Sciences Group, 1977.

Chapter in book with editor(s):

12. Pierce AK. Acute respiratory failure. In: Guenter CA, Welch MH, editors. Pulmonary medicine. Philadelphia: JB Lippincott, 1977.

**Tables.** Use consecutively numbered tables to display information. Start each table on a separate page. Number and title the table and give each column a brief heading. Place explanations in footnotes, including all nonstandard abbreviations and symbols. Key the footnotes with conventional designations (asterisk, dagger, double dagger, etc) in consistent order, placing them superscript in the table body. Do not use horizontal or vertical rules or borders. Do not submit tables as photographs, reduced in size, or on oversize paper. Use the same typeface as in the text.

**Illustrations.** Graphs, line drawings, photographs, and radiographs are figures. Use only illustrations that clarify and augment the text. Number them consecutively as Fig. 1, Fig. 2, and so forth according to the order by which they are mentioned in the text. Be sure all figures are cited. If any figure was previously published, include copyright holder's written permission to reproduce. Figures for publication must be of professional quality. Data for the original graphs should be available to the Editor upon request. If color is essential, consult the Editor for more information. In reports of animal experiments, use schematic drawings, not photographs. A letter of consent must accompany any photograph of a person. Do not place titles and detailed explanations on figures; put this information in figure captions. If possible, submit radiographs as prints and full-size copies of film.

**Drugs.** Identify precisely all drugs and chemicals used, giving generic names, doses, and routes of administration. If desired, brand names may be given in parentheses after generic names. Drugs should be listed on the product-sources page.

**Commercial Products.** In parentheses in the text, identify any commercial product (including model number if applicable) the first time it is mentioned, giving the manufacturer's name, city, and state or country. If four or more products are mentioned, do not list any manufacturers in the text; instead, list them on a Product Sources page at the end of the text, before the References. Provide model numbers when available and manufacturer's suggested price, if the study has cost implications.

**Ethics.** When reporting experiments on human subjects, indicate that procedures were conducted in accordance with the ethical standards of the institution's committee on human experimentation. State that informed consent was obtained. Do not use patient's names, initials, or hospital numbers in text or illustrations. When reporting experiments on animals, indicate that the institution's policy, a national guideline, or a law on the care and use of laboratory animals was followed.

**Statistics.** Identify the statistical tests used in analyzing the data, and give the prospectively determined level of significance in the Methods section. Report actual p-values in Results. Cite only textbook and published article references to support choices of tests. Identify any general-use or commercial computer programs used, naming manufacturers and their locations. These should be listed on the product-sources page.

**Units of Measurement.** Express measurements of length, height, weight, and volume in metric units appropriately abbreviated; temperatures in degrees Celsius; and blood pressures in millimeters of mercury (mm Hg). Report hematologic and clinical-chemistry measurements in conventional metric and in SI (Systémé Internationale) units. Show gas pressures (including blood gas tensions) in torr. List SI equivalent values, when possible, in brackets following non-SI values—for example, "PEEP, 10 cm $H_2O$ [0.981 kPa]." For conversion to SI, see RESPIRATORY CARE 1988;33(10):861-873 (Oct 1988) and 1989;34(2):145 (Feb 1989).

**Conflict of Interest.** Authors are asked to disclose any liaison or financial arrangement they have with a manufacturer or distributor whose product is part of the submitted manuscript or with the manufacturer or distributor of a competing product. (Such arrangements do not disqualify a paper from consideration and are not disclosed to reviewers.) A statement to this effect is included on the cover-letter page.

**Abbreviations and Symbols.** Use standard abbreviations and symbols. Avoid creating new abbreviations. Avoid all abbreviations in the title and unusual abbreviations in the abstract. Use an abbreviation only if the term occurs several times in the paper. Write out the full term the first time it appears, followed by the abbreviation in parentheses. Thereafter, employ the abbreviation alone. Never use an abbreviation without defining it. Standard units of measurement can be abbreviated without explanation (eg, 10 L/min, 15 torr, 2.3 kPa).

Please use the following forms: cm $H_2O$ (not cmH2O), f (not bpm), L (not l), L/min (not LPM, l/min, or lpm), mL (not ml), mm Hg (not mmHg), pH (not Ph or PH), $p > 0.001$ (not $p>0.001$), s (not sec), $S_{pO_2}$ (pulse-oximetry saturation).

## Submitting the Manuscript

Mail three copies of the manuscript, figures, diskette, and the Cover Letter & Checklist to RESPIRATORY CARE, 11030 Ables Lane, Dallas TX 75229-4593. Do not fax manuscripts. Protect figures with cardboard. Keep a copy of the manuscript and figures. Receipt of your manuscript will be acknowledged.

**Computer Diskettes.** A manuscript may be submitted on a Macintosh or IBM-DOS diskette. Macintosh documents on 3.5 in. diskettes written in Microsoft Word versions 4.0 and 5.0 are preferred. However, we can convert most documents (including PC-DOS format) to our format. Label each diskette with date; author's name; name of word-processing program and version used to prepare documents; and filename(s). Do not write on a diskette except with a felt-tipped pen. Tables and figures must be in their own separate files, with software identified. Supply 3 hard copies of the manuscript with the diskette.

**Prior and Duplicate Publication.** Work that has been published or accepted elsewhere should not be submitted. In special instances, the Editor may consider such material, provided that permission to publish is given by the author and original publisher. Please consult the Editor before submitting such work.

**Authorship.** All persons listed as authors should have participated in the reported work and in the shaping of the manuscript; all must have proofread the submitted manuscript; and all should be able to publicly discuss and defend the paper's content. A paper with corporate authorship must specify the key persons responsible for the article. Authorship is not justified solely on the basis of solicitation of funding, collection or analysis of data, provision of advice, or similar services. Persons who provide such ancillary services exclusively may be recognized in an Acknowledgments section.

**Permissions.** The manuscript must be accompanied by copies of permissions to reproduce previously published material (figures or tables); to use illustrations of, or report sensitive personal information about, identifiable persons; and to name persons in the Acknowledgments section.

**Reviewers.** Please supply the names, credentials, affiliations, addresses, and phone/fax numbers of three professionals whom you consider expert on the topic of your paper. Your manuscript may be sent to one or more of them for blind peer review.

## Editorial Office:

RESPIRATORY CARE
11030 Ables Lane
Dallas TX 75229-4593
(214) 243-2272 (telephone)
(214) 484-6010 (fax)

# Cover Letter & Checklist

A copy of this completed form must accompany all manuscripts submitted for publication.

Title of Paper: ______________________________

Publication Category: ______________________________

Authors: ______________________________

Author to be Contacted: ______________________________ Phone: ______________ FAX: ______________

Mailing Address of Contact Author: ______________________________

Reprints: ☐ Yes ☐ No

"We, the undersigned, have all participated in the work reported, proofread the accompanying manuscript, and approve its submission for publication." Please print and include credentials, title, institution, academic appointments, city and state. If more that 4 authors, please use another copy of this form.*

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Has this research been presented in a public forum? ☐ Yes ☐ No

If yes, where, when and by whom? ______________________________

Has this research received awards? ☐ Yes ☐ No

If yes, please describe. ______________________________

Do any of the authors have a financial interest in the products mentioned in this paper or competing products?

☐ Yes ☐ No If yes, please disclose: ______________________________

**Checklist:**

☐ Is double-spacing used throughout entire manuscript?
☐ Are all pages numbered in upper-right corners?
☐ Are all references, figures, and tables cited in the text?
☐ Has the accuracy of the references been checked, and are they correctly formatted?
☐ Have SI values been provided?
☐ Has all arithmetic been checked?
☐ Have generic names of drugs been provided?
☐ Have necessary written permissions been provided?
☐ Have authors' names been omitted from text and figure labels?
☐ Have copies of 'in press' references been provided?
☐ Has the manuscript been proofread by all the authors?

# Notices

Notices of competitions, scholarships, fellowships, examination dates, new educational programs, and the like will be listed here free of charge. Items for the Notices section must reach the Journal 60 days before the desired month of publication (January 1 for the March issue, February 1 for the April issue, etc). Include all pertinent information and mail notices to RESPIRATORY CARE Notices Dept, 11030 Ables Lane, Dallas TX 75229-4593.

## The National Board for Respiratory Care—1996 Examination Dates and Fees

| Examination | Examination Date | Examination Fee | |
|---|---|---|---|
| CRTT Examination | March 9, 1996 | $ 90 | (new applicant) |
| | Application Deadline: January 1, 1996 | 60 | (reapplicant) |
| | July 20, 1996 | 100 | (new applicant) |
| | Application Deadline: May 1, 1996 | 60 | (reapplicant) |
| | November 9, 1996 | 100 | (new applicant) |
| | Application Deadline: September 1, 1996 | 60 | (reapplicant) |
| RRT Examination | June 1, 1996 | 100 | Written only (new applicant) |
| | Application Deadline: February 1, 1996 | 60 | Written only (reapplicant) |
| | | 110 | CSE only (all applicants) |
| | December 7, 1996 | 210 | Both (new applicant) |
| | Application Deadline: August 1, 1996 | 170 | Both (reapplicant) |
| CPFT Examination | June 1, 1996 | 110 | (new applicant) |
| | Application Deadline: April 1, 1996 | 80 | (reapplicant) |
| RPFT Examination | December 7, 1996 | 160 | (new applicant) |
| | Application Deadline: September 1, 1996 | 130 | (reapplicant) |
| Perinatal/Pediatric Respiratory Care | March 9, 1996 | 160 | (new applicant) |
| | Application Deadline: November 1, 1995 | 130 | (reapplicant) |

For information about other services or fees, write to the
National Board for Respiratory Care, 8310 Nieman Road, Lenexa KS 66214, or call (913) 599-4200.

## Internet Access to the FDA http://www.fda.gov

The FDA Internet Home Page provides information on food, human and animal drugs, biologics, medical devices, the latest press releases, *Enforcement Reports*, and *Federal Register* notices. The Internet address can also connect information highway users to consumer education materials, industry guidance, bulletins for health professionals, the agency's bulletin board, full-text searches, and links to other FDA documents and government Internet sites.

If an Internet connection is not available or for information on how to connect to the FDA Home Page, call (301) 443-4908 between 7 AM and 5:30 PM EST.

## Now Available from the FDA: Information Sheets for IRBs & Clinical Investigators

The FDA now offers new information sheets to help institutional review boards (IRBs) and clinical investigators; the sheets are a revision of information previously issued in 1984 and 1989. The information sheets include: answers to questions frequently asked of the FDA, on drugs and biologicals, medical devices, FDA on-site inspections, and more.

For a copy, contact the Health Assessment Policy Staff, Office of Health Affairs, (301) 443-1382, or access the FDA's Internet Home Page at http://www.fda.gov.

# MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

For VOLUNTARY reporting
by health professionals of adverse
events and product problems

Page ___ of ___

Form Approved OMB No 0910-0291 Expires 1/31/96
See OMB statement on reverse

FDA Use Only (RESP CARE)

Triage unit
sequence #

## A. Patient information

| 1. Patient identifier | 2. Age at time of event: | 3. Sex | 4. Weight |
|---|---|---|---|
| In confidence | or<br>Date of birth: | ☐ female<br>☐ male | ____ lbs<br>or<br>____ kgs |

## B. Adverse event or product problem

1. ☐ **Adverse event** and/or ☐ **Product problem** (e.g., defects/malfunctions)

2. **Outcomes attributed to adverse event** (check all that apply)

- ☐ death ________ (mo/day/yr)
- ☐ life-threatening
- ☐ hospitalization – initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☐ other ________

3. **Date of event** (mo/day/yr)

4. **Date of this report** (mo/day/yr)

5. **Describe event or problem**

6. **Relevant tests/laboratory data,** including dates

7. **Other relevant history, including preexisting medical conditions** (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

## C. Suspect medication(s)

1. **Name** (give labeled strength & mfr/labeler, if known)
#1
#2

2. **Dose, frequency & route used**
#1
#2

3. **Therapy dates** (if unknown, give duration)
from/to (or best estimate)
#1
#2

4. **Diagnosis for use** (indication)
#1
#2

5. **Event abated after use stopped or dose reduced**
#1 ☐ yes ☐ no ☐ doesn't apply
#2 ☐ yes ☐ no ☐ doesn't apply

6. **Lot #** (if known)
#1
#2

7. **Exp. date** (if known)
#1
#2

8. **Event reappeared after reintroduction**
#1 ☐ yes ☐ no ☐ doesn't apply
#2 ☐ yes ☐ no ☐ doesn't apply

9. **NDC #** (for product problems only)
– –

10. **Concomitant medical products** and therapy dates (exclude treatment of event)

## D. Suspect medical device

1. **Brand name**

2. **Type of device**

3. **Manufacturer name & address**

4. **Operator of device**
- ☐ health professional
- ☐ lay user/patient
- ☐ other ________

5. **Expiration date** (mo/day/yr)

6.
model # ________
catalog # ________
serial # ________
lot # ________
other # ________

7. **If implanted, give date** (mo/day/yr)

8. **If explanted, give date** (mo/day/yr)

9. **Device available for evaluation?** (Do not send to FDA)
☐ yes ☐ no ☐ returned to manufacturer on ________ (mo/day/yr)

10. **Concomitant medical products** and therapy dates (exclude treatment of event)

## E. Reporter (see confidentiality section on back)

1. **Name & address**

**phone #**

2. **Health professional?**
☐ yes ☐ no

3. **Occupation**

4. **Also reported to**
- ☐ manufacturer
- ☐ user facility
- ☐ distributor

5. **If you do NOT want your identity disclosed to the manufacturer, place an " X " in this box.** ☐

FDA

Mail to: MEDWATCH
5600 Fishers Lane
Rockville, MD 20852-9787

or FAX to:
1-800-FDA-0178

FDA Form 3500 (6/93)

**Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.**

# ADVICE ABOUT VOLUNTARY REPORTING

**Report experiences with:**

- medications (drugs or biologics)
- medical devices (including in-vitro diagnostics)
- special nutritional products (dietary supplements, medical foods, infant formulas)
- other products regulated by FDA

**Report SERIOUS adverse events. An event is serious when the patient outcome is:**

- death
- life-threatening (real risk of dying)
- hospitalization (initial or prolonged)
- disability (significant, persistent or permanent)
- congenital anomaly
- required intervention to prevent permanent impairment or damage

**Report even if:**

- you're not certain the product caused the event
- you don't have all the details

**Report product problems** – quality, performance or safety concerns such as:

- suspected contamination
- questionable stability
- defective components
- poor packaging or labeling
- therapeutic failures

**How to report:**

- just fill in the sections that apply to your report
- use section C for all products except medical devices
- attach additional blank pages if needed
- use a separate form for each patient
- report either to FDA or the manufacturer (or both)

**Important numbers:**

| | |
|---|---|
| • 1-800-FDA-0178 | to FAX report |
| • 1-800-FDA-7737 | to report by modem |
| • 1-800-FDA-1088 | to report by phone or for more information |
| • 1-800-822-7967 | for a VAERS form for vaccines |

**If your report involves a serious adverse event with a device** and it occurred in a facility outside a doctor's office, that facility may be legally required to report to FDA and/or the manufacturer. Please notify the person in that facility who would handle such reporting.

**Confidentiality:** The patient's identity is held in strict confidence by FDA and protected to the fullest extent of the law. The reporter's identity, including the identity of a self-reporter, may be shared with the manufacturer unless requested otherwise. However, FDA will not disclose the reporter's identity in response to a request from the public, pursuant to the Freedom of Information Act.

The public reporting burden for this collection of information has been estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send your comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Reports Clearance Officer, PHS
Hubert H. Humphrey Building,
Room 721-B
200 Independence Avenue, S.W
Washington, DC 20201
ATTN: PRA

and to:
Office of Management and Budget
Paperwork Reduction Project
(0910-0291)
Washington, DC 20503

**Please do NOT return this form to either of these addresses.**

U S DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service • Food and Drug Administration

FDA Form 3500-back

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Public Health Service
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Rockville, MD 20857

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**The FDA Medical Products Reporting Program**
**Food and Drug Administration**
**5600 Fishers Lane**
**Rockville, MD 20852-9787**

Not-for-profit organizations are offered a free advertisement of up to eight lines to appear, on a space-available basis, in Calendar of Events in RESPIRATORY CARE. Ads for other meetings are priced at $5.50 per line and require an insertion order. Deadline is the 20th of the month two months preceding the month in which you wish the ad to run. Submit copy and insertion orders to Calendar of Events, RESPIRATORY CARE, 11030 Ables Lane, Dallas TX 75229-4593.

# Calendar of Events

## AARC & Affiliates

**May 15–17—Southwest Region of the Texas Society**
"25 Years of Excellence" Seminar at the El Paso Airport Hilton, El Paso, Texas.
CRCE: credit requested.
Contact: Maria Soto, Mobile Diagnostics, at (915) 593-3519.

**May 18–21—Washington Society**
23rd Annual Pacific Northwest Regional Respiratory Care Conference at Cavanaugh's Inn at the Park, Spokane, Washington.
Contact: Bob Bonner, Chair of the Health, Education and PE Division, Highline Community College, PO Box 98000, Des Moines WA 98198, (206) 878-3710, ext 3469.

**May 21—AARC Video Conference**
"Managing Demand for Respiratory Care Services," Part 3 of the 1996, 7-part video conference, "Professor's Rounds in Respiratory Care" from 12:30 to 2 PM Eastern Time. Live telephone question-and-answer session on June 10.
CRCE: 1 hour.
Contact: AARC at (214) 243-2272.

**May 21–23—Arizona Society**
Annual Education Seminar at the Phoenix Civic Plaza in downtown Phoenix, Arizona.
Contact: ASRC, 3900 E Camelback Rd, Suite 200, Phoenix AZ 85018, (602) 912-5300.

**May 23–25—Colorado Society**
Annual Conference, "Carrying the Torch," at the Marriott Vail Mountain Resort in the Colorado Mountains, Vail, Colorado.
Speakers: Dr Forrest Bird and Dr Martin Zamora.
Contact: Jill Brown at (303) 352-6082 ext 210 or Phil Goodman at (303) 436-6846.

**June 10–14—Florida Society**
1996 Sunshine Seminar at the Fountain Blue Hilton Resort & Towers, Miami Beach, Florida.
Contact: Deborah Herrick at (305) 587-5010 or fax at (305) 583-2927.

**June 19–21—Oklahoma Society**
31st Annual Seminar at the Radisson Inn, Oklahoma City, Oklahoma.
Contact: Gennie Ridlen at (405) 680-2154.

**July 9—AARC Video Conference**
"Capturing Respiratory Services Outside the Hospital Part I: Home Care," Part 4 of the 1996, 7-part video conference, "Professor's Rounds in Respiratory Care"
from 12:30 to 2 PM Eastern Time. Live telephone question-and-answer session airs July 29.
CRCE: 1 credit hour.
Contact: AARC at (214) 243-2272.

**July 17–19—Texas Society**
Annual Convention, "Upgrade Your Memory," at the Wyndham Anatole Hotel, Dallas, Texas.
CRCE: credit requested.
Contact: TSRC at (214) 680-2454.

## Other Meetings

**May 31–June 2—University of Virginia and Medical College of Virginia ECMO Programs**
6th Annual Southeastern ECMO Conference at the Hyatt Regency, Richmond, Virginia.
Contact: Bobbi Ksenich, University Health Sciences Center, NICU, 7 East, Charlottesville VA 22908, or call Gail Allen at (804) 828-2754.

**June 26–29—ECMO Programs**
5th European Extracorporeal Support Organization Conference, Stockholm, Sweden.
Contact: the Congress Secretariat at +46 8 612 6900 or fax +46 8 612 6292.

**September 18–21—Costa Rica Society for Respiratory Therapy**
2nd Latin America Congress and the 4th Central America and Caribbean Congress for Respiratory Therapy, "Advances in Respiratory Therapy" in San José, Costa Rica.
Contact: Isabel Mesen-Sequeira, administrative assistant, PROJECTHOPE, SJO 078, PO Box 025369, Miami FL 33102, 011-506-290-4242, fax 011-506-296-3531.

**September 19–21—ECMO Programs**
8th Extracorporeal Life Support Organization Conference at the Ritz Carlton, Dearborn, Michigan.
Contact: Phoebe Hankins at (313) 998-6600.

**October 23–25—ECMO Programs**
10th Western ECMO Conference, Rancho Mirage, California.
Contact: Janie Waggoner of the Loma Linda ECMO Program at (909) 478-8781.

**November 10–14—Asia Pacific Association for Respiratory Care**
5th Congress of APARC at the Bangkok Convention Centre and Central Plaza Hotel, Bangkok, Thailand.
Abstracts must be submitted by July 31.
Contact: Congress Secretariat, 5th Congress of APARC, Congress and Convention Experts (Thailand) Co Ltd, PO Box 10-163, Ladphrao, Bangkapi, Bangkok 10310, THAILAND.

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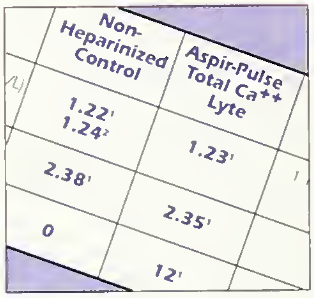

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